

















**National Institutes of Health (U.S.)**

**Office of the Director**

**SPEECHES, ARTICLES, AND SELECTED PAPERS**

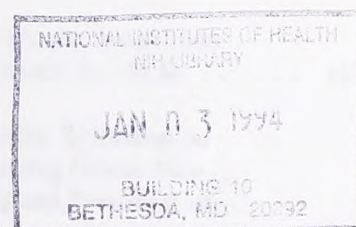
**By**

**James B. Wyngaarden, M.D.**

**1982-1988**

**Volume 3 (of 5)**

**(January 18, 1985—December 5, 1986)**





RA

11

D63305

1982-88

v. 3



**Speeches, Articles, and Selected Papers**  
**James B. Wyngaarden, M.D.**

1982-1988  
Volume 3

<u>Date</u>	<u>Place</u>	<u>Title and audience</u>	<u>Doc.</u>
1/18/85	NIH	Introductory Remarks, Introduction of Senator Julian Bond, Dr. Martin Luther King Birthday Observance . . . . .	153
1/25/85	Chapel Hill, NC	On Excellence and Creativity, University of North Carolina School of Medicine's Student Research Day . . . . .	154
1/30/85	NIH	Welcoming Remarks, Conference for Directors of Minority Institutions . . . . .	155
2/20/85	San Francisco, CA	Directions and Challenges for Biomedical Research, Symposium on Genetics and Nutrition: Relevance to Learning Disabilities . . . . .	156
3/4/85	Washington, DC	Address, 44th Annual Science Talent Search by Westinghouse Educational Foundation . . . . .	157
3/9/85	Atlanta, GA	Address, Dedication of the Science Research Institute Facility at Atlanta University . . . . .	158
3/25/85	NIH	Introduction of Senator Jacob Javits, NINCDS All Employees Meeting . . . . .	159
3/29/85	House of Representatives Washington, DC	Statement Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce . . . . .	160
4/4/85	Washington, DC	Institutional Impacts of NIH Initiatives and Reforms, Address Tenth Annual AAAS Colloquium on R&D Policy . . . . .	161
3/20/85	San Francisco, CA	UCSF as a Parnassus of Research, Symposium in Honor of Dr. Lloyd H. Smith, Jr., M.D. . . . .	162
4/18/85	NIH	Welcoming Remarks, NIADDK Workshop on Mapping, Cloning, Manipulating Genes: New Strategies for Understanding and Treatment of Inherited Human Diseases . . . . .	163







Speeches, Articles, and Selected Papers; James B. Wyngaarden, M.D., Vol. 3 (Cont.)

<u>Date</u>	<u>Place</u>	<u>Title and audience</u>	<u>Doc.</u>
4/24/85	Anaheim, CA	NIH - After Almost a Century of Science for Health, American Society of Biological Chemists at FASEB Meetings . . . . .	164
5/1/85	NIH	Introductory Remarks for Dr. Louis Miller, Dyer Lecture . . . . .	165
5/13/85	NIH	Welcoming Remarks, Donor Registries for Bone Marrow Transplantation Conference . . . . .	166
5/21-25/85	Copenhagen, Denmark	Introductory Remarks, EMRC Conference on "Methodologies in Technology Assessment" . . . . .	167
6/6-7/85	NIH	Remarks, National Library of Medicine Board of Regents 79th Meeting . . . . .	168
6/7/85	Ann Arbor, MI	Personal Creativity and Professional Citizenship, Address at the University of Michigan Medical School . . . . .	169
6/17/85	NIH	Opening Remarks, NIH Honor Awards Ceremony . . . . .	170
6/24/85	NIH	Opening Statement, Director's Advisory Committee Meeting . . . . .	171
6/25/85	Washington, DC	After-dinner Address, Conference on the Health Effects of Polyunsaturated Fatty Acids in Seafoods . . . . .	172
7/8/85	NIH	Welcoming Remarks, Orientation of Medical Staff Fellows . . . . .	173
7/12/85	New York, NY	The Federal-Private Partnership in Aging Research, American Federation for Aging Research Awards Luncheon . . . . .	174
7/13/85	New York, NY	Address, Plenary Session of XIIIth International Congress of Gerontology . . . . .	175
7/24/85	London, England	Research in the USA, Royal Society of Medicine Anglo-American Conference on Clinical Investigation of Infectious Diseases . . . . .	176







Speeches, Articles, and Selected Papers; James B. Wyngaarden, M.D., Vol. 3 (Cont.)

<u>Date</u>	<u>Place</u>	<u>Title and audience</u>	<u>Doc.</u>
8/19/85	NIH	Remarks, Reception for NIH Special Police and Those Involved in Protecting NIH and the NINCDS Employees at the Time of the Building 31 Demonstration by the Animal Rights Activists . . . . .	177
9/7/85	New York, NY	Address, Hartford Foundation Scholars Program . . . . .	178
9/9/85	NIH	Welcoming Remarks to the Secretary, On the Occasion of the Consensus Development Conference on Adjuvant Chemotherapy for Breast Cancer . . . . .	179
9/23/85	Montreal, Canada	The Role of Government Support in Biomedical Research, Address Given at the International Symposium in Honor of Jacques Genest . . . . .	180
9/26/85	Senate, Washington, DC	Statement Before the Subcommittee on Labor-HHS-Education Committee on Appropriations . . . . .	181
10/1/85	NIH	Remarks, Groundbreaking Ceremony for the Cloister at the Mary Woodard Lasker Center for the HHMI-NIH Scholars Program . . . . .	182
10/2/85	New Haven, CT	Funding of Biological Research, Address Given at Seminar on Biology . . . . .	183
10/5/85	Chicago, IL	NIH Support of Research and Research Training in Neurobiology, Address the American Neurological Association Meeting . . . . .	184
10/7/85	Bethesda, MD	Remarks, Opening Address, NIH-UCSF Conference on Ethics Consultation in Health Care . . . . .	185
10/10/85	Washington, DC	Address, Presented at the Industrial Biotechnology Association Annual Meeting . . . . .	186







Speeches, Articles, and Selected Papers; James B. Wyngaarden, M.D., Vol. 3 (Cont.)

<u>Date</u>	<u>Place</u>	<u>Title and audience</u>	<u>Doc.</u>
10/20/85	Kyoto, Japan	Comments, Acceptance of Stone Lantern Presented by Professor Kozo Okamoto to the National Institutes of Health, 5th International Symposium on SHR and Related Studies . . . . .	187
10/28/85	Coconut Grove, FL	The Government's Response to the AIDS Crisis, Howard Hughes Medical Institute Conference on Retroviruses and Immunosuppression . . . . .	188
10/30/85	House of Representatives Washington, DC	Statement Before the Subcommittee on Science, Research, and Technology of the Committee on Science and Technology . . . . .	189
11/4/85	Monaco	Progress and Promise in Diabetes Research, Keynote Address at the Juvenile Diabetes Foundation International World Conference on Diabetes Research . . . . .	190
11/13/85	Bethesda, MD	Welcoming Remarks to the Secretary, Secretary Heckler's Conference on Breast Cancer . . . . .	191
11/14/85	U.S. Congress Washington, DC	Statement Before the Environmental and Energy Study Conference . . . . .	192
11/14/85	NIH	Remarks, Director Honor Awards Ceremony . . . . .	193
11/15/85	New York, NY	Federal Biomedical Science Policy, The New York Science Policy Association, New York Academy of Sciences . . . . .	194
11/19/85	Morgantown, WV	Frontiers in Medicine and Medical Research, Presented at the School of Medicine, West Virginia University . . . . .	195
12/4/85	NIH	Comments, Dr. Edward Korn on the Occasion of the Mider Lecture . . . . .	196
12/10/85	NIH	Introductory Remarks for the December 16 Director's Advisory Committee Meeting . . . . .	197







Speeches, Articles, and Selected Papers; James B. Wyngaarden, M.D., Vol. 3 (Cont.)

<u>Date</u>	<u>Place</u>	<u>Title and audience</u>	<u>Doc.</u>
12/18/85	Atlanta, GA	Clinical Research and Cost-Effective Health Care, Clinical Research Center at Emory University in Atlanta . . . . .	198
3/5/86	NIH	Statement of the Director, National Institutes of Health . . . . .	199
3/10/86	NIH	Statement of the Director, 1986 Budget Hearings . . .	200
3/24/86	Rosslyn, VA	Remarks, Luncheon for the Women in Science and Engineering (WISE) Award . . . . .	201
3/25/86	Washington, DC	The National Institutes of Health at the Crossroads, 33rd National Health Forum . . . . .	202
3/31/86	NIH	Welcoming Remarks, 1986 Savings Bond Campaign Bond Campaign for Canvassers and Coordinators . . .	203
4/2/86	-	Remarks, NIH Centennial Committee Dinner . . . . .	204
4/4/86	Washington, DC	Clinical Investigation: NIH Perspective, Second National Conference on Research Goals and Methods for Otolaryngology-Head and Neck Surgery . . . . .	205
4/8/86	Florence, SC	A Look into the Future -- New Advances in Health Care, 37th Annual McLeod Seminar . . . . .	206
4/10/86	Palo Alto, CA	Biomedical Research, NIH and the Budget, AAAS Pacific Division Conference . . . . .	207
4/17/86	Senate, Washington, DC	Statement on Seafood and Health Before the Committee on Commerce, Science, and Transportation	208
4/24/86	Heidelberg, Germany	Certain Aspects of Medical Research and Its Support, 600th Anniversary Symposium at the University of Heidelberg . . . . .	209
4/30/86	Bethesda, MD	Remarks, National Diabetes Research Interchange . . . . .	210
5/6-8/86	-	Task Force on Science Policy, Hearing on the Future of the National Academies . . . . .	211





Speeches, Articles, and Selected Papers; James B. Wyngaarden, M.D., Vol. 3 (Cont.)

<u>Date</u>	<u>Place</u>	<u>Title and audience</u>	<u>Doc.</u>
5/14/86	Washington, DC	A Look Toward the Future of the Health Sciences, Semi-Annual Meeting of the Council of Scientific Society Presidents . . . . .	212
5/19/86	NIH	Introductory Remarks, Dr. Philip Leder at an NIH Lecture . . . . .	213
5/28/86	New York, NY	Research: International Cooperation and Competition, Symposium on "AIDS: Impact on Public Policy" . . . . .	214
5/30/86	Washington, DC	Medicine as Art: Medicine as Science, Commencement Address Given at the George Washington University School of Medicine and Health Sciences . . . . .	215
6/5-6/86	London, England	Report on NIH Activities, Meeting of the European Medical Research Council . . . . .	216
6/16/86	NIH	Remarks, 1986 NIH Honor Awards Ceremony . . . .	217
6/19/86	NIH	Remarks, Dedication and Ribbon-Cutting of the Newly Renovated Building 8 . . . . .	218
7/2/86	NIH	Remarks, Dedication of the Japanese Stone Tower at NIH in Honor of Professor Kozo Okamoto of Kinki University . . . . .	219
7/7/86	NIH	Welcoming Remarks, Orientation of Medical Staff Fellows . . . . .	220
7/11/86	New York, NY	Federal Biomedical Research Policy, 1986; Memorial Sloan Kettering Cancer Center . . . . .	221
8/5/86	Woods Hole, MA	Alternative Uses of Funds and Personnel, NRC Meeting Remapping and Sequencing the Human Genome . . . . .	222
8/21/86	Budapest, Hungary	Opening Remarks, 14th International Cancer Congress . . . . .	223
9/16/86	NIH	Colloquium on the Future of Biomedical Communication NLM Sesquicentennial Celebration . . . . .	224





Speeches, Articles, and Selected Papers; James B. Wyngaarden, M.D., Vol. 3 (Cont.)

<u>Date</u>	<u>Place</u>	<u>Title and audience</u>	<u>Doc.</u>
9/22/86	San Juan, Puerto Rico	Nurturing the Biomedical Research Enterprise, University of Puerto Rico Medical Sciences Campus . . . . .	225
9/25/86	Bethesda, MD	Opening Remarks, NIH Research Day . . . . .	226
9/25/86	Bethesda, MD	Fiscal Future of Biomedical Research, Opening Remarks at the Workshop for Medical Staff Fellows . . . . .	227
9/26/86	San Antonio, TX	Support of Biomedical Research in the Late 1980's, Clinical Immunology Research Conference . . . . .	228
10/7/86	Copenhagen, Denmark	Introductory Remarks, Joint Meeting of the WHO, European Research Council and NIH . . . . .	229
10/15/86	Washington, DC	Current Status of Treatment of Genetic Disease, Institute of Medicine Annual Meeting . . . . .	230
10/16/86	NIH	Background and Purpose of Centennial Observance, Opening Ceremony of the NIH Centennial Observance . . . . .	231
10/16-17/86	NIH	Introductory remarks, Advisory Committee to the Director . . . . .	232
10/20/86	Bethesda, MD	Welcoming Remarks, NIAMS/NAAB Conference on "Molecular Biology: Its Potential for Advancing Rheumatology Research" . . . . .	233
10/24/86	San Francisco, CA	Keynote Address, The Impact of New Imaging Technology on Health Care, Research, and Teaching . . . . .	234
10/27/86	New Orleans, LA	Remarks, Annual AAMC Meeting . . . . .	235
11/6/86	Washington, DC	Multidimensional Cooperation in Biomedical Research, Montedison Conference on Science and Technology: Between International Cooperation and Competition . . . . .	236
11/9/86	Boston, MA	The Quest for New Knowledge, American Association of University Affiliated Programs for Persons with Developmental Disabilities . . . . .	237





Speeches, Articles, and Selected Papers; James B. Wyngaarden, M.D., Vol. 3 (Cont.)

<u>Date</u>	<u>Place</u>	<u>Title and audience</u>	<u>Doc.</u>
11/10/86	Boston, MA	Nurturing the NIH-Industrial Linkage, 1987 Fall Meeting of the Industrial Research Institute . . .	238
12/3/86	Research Triangle Park, NC	The Evolution of Science at the National Institutes of Health and the National Institutes of Environmental Health Sciences, Scientific Seminar, "The Environment and Human Health: Achievements and New Directions" . . . . .	239
12/5/86	Research Triangle Park, NC	The Genesis of the National Institutes of Health, 20th Anniversary Ceremony of the National Institute of Environmental Health Sciences . . . . .	240





## INTRODUCTORY REMARKS\*

by

James B. Wyngaarden\*\*

Each year since 1973, the National Institutes of Health has sponsored a program of remembrance with a rededication to the principles so effectively put forward in word and deed by Dr. Martin Luther King, Jr. Held on the day or within the week of Dr. King's birthday, these annual observances have been highlight occasions addressed by some of America's best known leaders. Today is no exception.

Our speaker is a man whose career has been dedicated to the fight for civil rights. Although he is a young man, the record of his accomplishments is full. He was a leader and founder of the Student Nonviolent Coordinating Committee at Morehouse College in the early 1960s, participating in voting drives, sit-ins, and other activities of that moment until his campaign for State Representative. He was first elected to the Georgia House of Representatives in 1965 but was prevented from taking office in January 1966 by members of the Legislature who objected to his statement about the war in Vietnam. After winning a second election in February 1966, a House Committee again voted to bar him from membership. He won a third election in November 1966, and

---

\*Introduction of Senator Julian Bond, Dr. Martin Luther King Birthday Observance, Masur Auditorium, January 18, 1985.

\*\*Director, National Institutes of Health, Bethesda, Maryland.

after a unanimous U.S. Supreme Court ruling that the Georgia House was in error in refusing to seat him, Julian Bond was sworn in on January 9, 1967, as a member of the George House. He became a member of the Georgia Senate in 1975.

Senator Bond has received many honors (more than 10 honorary doctorates) and is the leader of a number of influential groups active in the cause of human rights.

He is known as a man who fights within the political system for the rights of the neglected, and judging from his first 44 years, I am certain that this country will hear much more from Senator Julian Bond.

It is a great pleasure to present Senator Bond.



## "ON EXCELLENCE AND CREATIVITY"\*

by

JAMES B. WYNGAARDEN, M.D.\*\*

For several good reasons, it is a special pleasure for me to be a participant in Student Research Day at the University of North Carolina School of Medicine. I am flattered that the students responsible for this occasion invited me to have a part in it and, in doing so, have classed me with the distinguished company whose members have been selected for this honor previously. Furthermore, my relatively brief journey into the wilds of bureaucracy thus far has not diminished my affection for the academic enterprise. But neither has it permitted me to engage directly in research. Consequently, I have a warm glow of nostalgia in a setting like this, enhanced, of course, by the fact that much of my professional life has been invested in your neighboring institution at the Durham vertex of the research triangle.

Before embarking upon my prepared address, I want to tell your group about an exciting discovery recently made at the NIH on the mechanism of hibernation. It seems that in the fall the bears line up in order of height and size, and head single file for the nearest cave. The smallest bear enters first, followed by the next larger, and the next, and so on, until the largest bear of all enters the cave, stands up in the entrance way obliterating all the light and says, "First slide, please." That story is by way of announcing that I will have no slides to show, since in my experience slides after a dinner are an invitation to acute episodes of temporary hibernation.

However, I do wish to express a few thoughts on the quality of excellence and on its logical companion--creativity, of which this afternoon's presentations were splended examples.

The word "excellence" implies competition--"doing better than." Strictly speaking, it is not possible to describe excellence in a vacuum. If we say that something or someone is excellent, the statement has little meaning unless we can supply the context--"compared with what?" For the individual, we usually make the obvious comparison--that is, competition with others--as our standard of excellence.

We often allude to universities or research institutions as "centers of excellence." In doing so, we are describing more than a magnificent facility populated by a community of distinguished scientists and educators. The "excellence" in such centers is much more likely to be the result of constant interaction that draws out from students, scientists, and faculty alike the extra effort and dedication that would not be demanded in a less competitive setting.

---

\*Presented at the University of North Carolina School of Medicine's Student Research Day, Chapel Hill, North Carolina, January 25, 1985.

\*\*Director, National Institutes of Health, Bethesda, Maryland.

This, by the way, is why such great care is exercised in selecting students for admission to medical or graduate school. The quality of a school is to a very great extent determined by the quality of students it accepts. Interactions among students are such that an outstanding freshman class tends to be an outstanding graduating class--and, in addition, it will have a stimulating influence on all its contemporaries for its four-year life.

Lewis Thomas, in looking back on his own experience as a medical student, attributed much of his education to his fellow students. In his book on "The Youngest Science," Dr. Thomas remarked, "When I am asked . . . which member of the Harvard faculty had the greatest influence on my education in medicine, I no longer grope for a name on that distinguished roster. What I remember now from this distance is the influence of my classmates. We taught each other; we may even have set careers for each other without realizing at the time that so fundamental an educational process was even going on."<sup>1</sup>

I need not tell you that your admission to medical school was competitive--requiring a high degree of demonstrated excellence. Such excellence was judged in large measure by your success in coping with baccalaureate academic requirements. More than most, medical students can appreciate the aptness of the word "curriculum." The word conveys the image of a racetrack through its Latin root--the verb meaning "to run."

During your sprints in running the race courses--the curricula required for graduation--you are constantly reminded by your coaches, as well as by your competitors, of the pace required of those who would excel. But as you progress in your postdoctoral training, you will become more of a lonely long-distance runner and you will set your own pace. You will no longer be running in competition with others so much as you will be competing against your own standards; running to reach your own potential.

As we advance in training and experience, this set of self-generated standards comes into play for each of us, for it is then that our personal definition of excellence and our responses to it determine the level of our competence to fulfill the high promise with which our careers of service were begun. The answer to the question "compared with what?" ultimately becomes an expression of our personal goals.

What is the source of these internal standards? I personally believe the excellence genes are far more widely distributed in the population than is generally realized and, as my grandmother used to say, some genes are inherited. One of the functions of education is to make it possible for individuals to achieve in ways they thought were beyond their capabilities. This takes place largely through the generation and nurture of an appreciation of excellence.



In his essays on "The Aims of Education," Alfred North Whitehead used the term "culture" in discussing the development of the consciousness of quality which is the essential element of any personal standard of excellence--whether for doctor, lawyer, teacher, or priest.

"Culture," he said, "is activity of thought and receptiveness to beauty and humane feeling. Scraps of information have nothing to do with it. A merely well-informed man (or woman) is the most useless bore on God's earth. What we should aim at producing is men (and women) who possess both culture and expert knowledge in some direction. Their expert knowledge will give them the ground to start from and their culture will lead them as deep as philosophy and as high as art. We have to remember that the valuable intellectual development is self-development."<sup>2</sup>

In 1978, the presidents of 15 leading American universities jointly authored a report called "Research Universities and the National Interest." In the report, the presidents made a general statement which, without mentioning the word, is a commentary on excellence.

"First-rate work in any field of human action is rare and difficult," they said, "but nowhere is the quality of work more decisive than in higher learning and research. It is hard to tell in advance who will do first-class scholarly and scientific work. Sometimes such work is recognized only slowly. Moreover, when a problem is extraordinarily resistant, even first-class work can fail. But none of these qualifications detracts from the force of the proposition that it is quality that counts." In the simple words of the late Philip Handler, "In science, the best is vastly more important than the next best."<sup>3</sup> The same could surely be said of the practice of medicine.

John Gardner remarked that "Commencement speakers are fond of saying that education is a lifelong process. And yet," he added, "that is something that no young person with a grain of sense needs to be told." He then asked, "Why do speakers go on saying it?" And supplied an answer, "It isn't that they underestimate their audience. The truth is that they know something their young listeners do not know--something that can never be fully communicated.

"No matter how firm an intellectual grasp the young person may have on the idea that education is a lifelong process, he can never know it with the poignancy, with the deeply etched clarity, with the overtones of satisfaction and regret that an older person knows it. The young person has not yet made enough mistakes that cannot be repaired. He has not yet passed enough forks in the road that cannot be retraced."

Then Gardner added that "The commencement speaker may give in to the temptation to make it sound as though the learning experiences of

the older generation were all deliberate and a triumph of character--character that the younger generation somehow lacks. It is not easy," Gardner says, "to tell young people how unpurposefully we learn, how life tosses us head-over-heels into our most vivid learning experiences, how intensely we resist many of the increments in our own growth."<sup>4</sup>

Sheer talent does not equate to excellence. Keeping fully informed is essential but does not guarantee maintenance of excellence. Unless it is put to risk in performance, excellence soon fades. It is ultimately the quality of performance that counts.

The term "creativity" almost inevitably comes to mind when thinking about excellence. Basically, "to create" is to generate something that did not previously exist. But creativity is not easy to define. The dictionary lists such synonyms as originality, inventiveness, productivity, ingenuity, and novelty. These terms imply new insights, new associations, relationships, and interpretations. They imply discovery plus integration into a larger body of knowledge, the evolution of new perceptions, perhaps of new paradigms. For those who are not acquainted with the book, I recommend Thomas Kuhn's, The Structure of Scientific Revolutions, in which he develops the theme that science grows not by continuous smooth expansion but rather by the development of new paradigms, new insights that give rise to new operational tenets that give new directions to emerging fields.

Creativity takes many forms. Wherever it is applied--in the practice of medicine--in research--in teaching--in administration--it carries with it the qualities of excellence, spirit of inquiry, and the application of curiosity and imagination.

Imagination is a kind of latent creativity. It is natural for young people to be imaginative and if this imagination can be coupled with discipline, its energy can be lifelong strength. Whitehead remarked that a "tragedy of the world is that those who are imaginative have but slight experience, and those who are experienced have feeble imagination." And that "fools act on imagination without knowledge, pedants act on knowledge without imagination."<sup>5</sup>

It is not easy to describe the process, creativity. Sir William Osler had his explanation for creative progress in medicine. He said, "A master word . . . is directly responsible for all advances in medicine over the past twenty-five centuries . . . The master word is "work."<sup>6</sup>

But in Sir Arthur Fleming's account of the discovery of penicillin, a dramatically different quality of creativity is suggested; namely the role of chance. He said, "There are thousands of different molds and there are thousands of different bacteria, and that chance put that mold in the right spot at the right time is like winning the Irish Sweepstakes."<sup>7</sup>



The great French scientist, Claude Bernard, anticipated Fleming's comment about the accidental nature of creativity but added another important dimension to the thought. Bernard said that "Experimental ideas are very often born by chance as the result of fortuitous observations . . . we walk, so to speak, in the realm of science and we pursue what happens to present itself accidentally to our eyes."<sup>8</sup> The same idea was economically expressed by Franklin P. Adams when he said, "I find that a great part of the information I have was acquired by looking up something and finding something else on the way."<sup>9</sup> Perhaps it is useful to emphasize that both Bernard and Adams linked creativity to activity. Serendipity is a dividend of action.

Any discussion of the role of chance as it relates to creativity in science is incomplete without the moderating words of Louis Pasteur, "Chance favors only the prepared mind."<sup>10</sup> Even before Pasteur, Joseph Henry, the American physicist, had noted that "The seeds of great discoveries are constantly floating around us, but they only take root in minds well prepared to receive them."<sup>11</sup> When the Belgian scientist, Géry Hers, was introduced to Carl Cori, the remark was made that Dr. Hers had a lot of luck in his work in Berkeley. "Luck does not exist," replied Carl Cori at once, "because it is always the same people who are lucky."<sup>12</sup>

It has been said that the two great enemies of creativity are mental rigidity on the one hand and wishful thinking on the other. These are evident when a person acts either in a far more regular way than the situation demands or else is incapable of perceiving the external realities that make his ideas infeasible. I will add a third enemy; namely, "imitation."

These barriers to creativity are of the utmost difficult kind because they are self-imposed. They tend to give undue importance to established patterns of thought and lock themselves into conformity with them. We fear to challenge the obvious lest we appear naive. For some, this fear may be an insurmountable barrier. Jacques Barzun once remarked that one cannot learn to ice skate or speak French without looking foolish, and that's why these skills are easy to the young who do not worry so much about appearances.<sup>13</sup>

Permit me to return, however, to the specifics of this occasion--to the implications of Student Research Day.

It is heartening to me that in the midst of a demanding schedule, a substantial number of medical students are attracted to research. For, in my view, one of our pressing needs is for physician-investigators.

The well-trained physician has valuable and unique insights to offer across the entire spectrum of biomedical research. It is for this reason that the National Institutes of Health has developed special research training programs for physicians. There simply isn't enough time in the medical school curriculum to give the kind



of research training that is essential for those who devote themselves to investigative work at the complex frontiers of today's medical science.

Notwithstanding the spectacular progress that has been made, medicine today still calls for better than our best. The major health care problem of our time lies in the continued existence of diseases for which we can do little. Even if the best of contemporary medicine were universally available without financial barriers, cancer would continue to kill, rheumatoid arthritis would continue to cripple, and schizophrenia would continue to render insane. Medicine as a science is far from complete. It will remain so, for science itself is by its nature incomplete. But science is not static. Medical science constantly moves forward--its motion fueled by the fresh insights of research scientists and alert practitioners.

Dr. Lewis Thomas has commented on the possible responses that modern medicine can make to the major disease problems that so far have resisted medical progress.

"The quick and easy way," he said, "is to conclude that these diseases not yet mastered are simply beyond our grasp. The thing to do is settle down with today's version of science and technology and make sure that our health care system is equipped to do the best it can in an imperfect world. The problem with this approach is that we cannot afford it. The costs are already too high and they escalate higher each year. Moreover, the measures available are simply not good enough. We cannot go on indefinitely trying to cope with heart disease by open heart surgery carried out at formidable expense after the disease has run its destructive course. Nor can we postpone such issues by oversimplifying the problems, which is what we do . . . by attributing so much of today's chronic and disabling disease to the environment or to wrong ways of living. The plain fact of the matter is that we do not know enough about the facts of the matter, and we should be more open about our ignorance."

But I would not wish to leave Lewis Thomas on this downbeat note. He went on to say paradoxically that there has never been a period in medicine when the future looked so bright, and I agree with him. He amplified this thought and I will close with his words: "There is within medicine," he said, "somewhere beneath the pessimism and discouragement resulting from the disarray of the health care system and its stupendous cost, an undercurrent of almost outrageous optimism about what may lie ahead for the treatment of human disease if we can only keep learning."<sup>14</sup>

X X X Y X

### References

- <sup>1</sup>Lewis Thomas, The Youngest Science, The Viking Press, New York, 1983, p. 29.
- <sup>2</sup>Alfred North Whitehead, "The Aims of Education," American Library of World Literature, Inc., New York, 1955, p. 13.
- <sup>3</sup>Research Universities and the American Interest, Ford Foundation, New York, 1978, p. 5
- <sup>4</sup>John W. Gardner, Excellence, Harper & Rowe, New York, 1962, pp. 138-139.
- <sup>5</sup>Alfred North Whitehead, op. cit., p. 98.
- <sup>6</sup>James H. Austin, Chase, Chance and Creativity, Columbia University Press, New York, 1978, p. 185.
- <sup>7</sup>Ibid., p. 89.
- <sup>8</sup>Ibid., p. 1.
- <sup>9</sup>Ibid., P. 8.
- <sup>10</sup>Judith P. Swazey and Karen Reeds, "Today's Medicine Tomorrow's Science," NIH 83-244, USDHHS, Washington, 1983, p. 7.
- <sup>11</sup>Ibid., p. 11.
- <sup>12</sup>Henri-Géry Hers, Selected Topics in the History of Biochemistry, Elsevier Science Publishers, New York, 1983, p. 78.
- <sup>13</sup>Jacques Barzun, Teacher In America, Doubleday and Co., New York, 1959, p. 124.
- <sup>14</sup>Lewis Thomas, The Medusa and the Snail, The Viking Press, New York, 1979, pp. 165-166.





## WELCOMING REMARKS\*

by

JAMES B. WYNGAARDEN, M.D.\*\*

It is a pleasure to welcome you to the National Institutes of Health and to thank you for coming here to advise and assist us in refining the guidelines for an important new program.

The establishment of awards for development of Research Centers in Minority Institutions was directed by the Congress in the course of appropriating our operating funds for Fiscal Year 1985.

The appropriation was made in the context of continued concern that although NIH funding for research at minority institutions has grown dramatically since the 1960's, these institutions have not shared adequately in the growth of the NIH extramural programs. This addition to the generally successful Minority Biomedical Research Support (MBRS) and Minority Access to Research Careers (MARC) programs represents a further strategy in our effort to strengthen the research capabilities of minority institutions.

I can recall hearing the basic idea discussed some two years ago when Dr. Malone, Dr. Raub, other members of the NIH staff, and I met here with representatives of the research committee of the National Association for Equal Opportunity. A similar theme was the focus of a meeting about that time between representatives of the Association of Minority Health Professions Schools and former Assistant Secretary Brandt and me. The suggestion was made to us that we might key new efforts to programs involving minority academic institutions offering doctoral-level health-related training. This general idea was transmitted in our February 1984 report to the Congress on NIH Initiatives With Respect to Historically Black Colleges and Universities. The concept was strongly reinforced in the testimony of the citizen witnesses who appeared before the Appropriations Committee. In the process of its consideration by the Committee, the basic idea was changed a bit and added to--but it emerged, and we are here today to consider how best to make the concept work.

We need your special insights--your advice on how a good idea can be translated into a valuable program. Acting on my conviction that the important speeches today will be made by nongovernment spokesmen, I will summarize by expressing in advance our appreciation for the help you will give us and, once again, extend a hearty welcome.

---

\*Presented at the Conference for Directors of Minority Institutions, National Institutes of Health, January 30, 1985.

\*\*Director, National Institutes of Health.



# "DIRECTIONS AND CHALLENGES FOR BIOMEDICAL RESEARCH"\*

by

JAMES B. WYNGAARDEN, M.D.\*\*

I would like first to express my sincere appreciation to the organizers of this important conference for honoring me as keynote speaker. I am pleased to address the issue of "Directions and Challenges for Biomedical Research" before such a prestigious body. In addition, the Association for Children and Adults with Learning Disabilities should be congratulated for their efforts at bringing together this group, which will cover many aspects of genetics and nutrition: their relevance to learning disabilities.

My predecessor, Donald S. Fredrickson, told a congressional committee some years ago that there are three great generic categories of inquiry in biomedical science. One, he said, is to understand biological systems. Another is to understand how the genetic code determines the fitness of individuals in regard to the functioning of their biological systems. The third, Fredrickson said:

"...is a question of how man and other animals adapt to the environment and ecology in which they live, and that adaptation is dependent both on the nature of the environment and on the genetic structure..."

All three categories of inquiry are vigorously pursued by the National Institutes of Health.

The support of basic research is a responsibility of Government, for the dual reasons that it benefits the people and the economy of the nation and that there is no other substantial source for its support. The bulk of support for basic biomedical research, conducted mainly in university laboratories, will continue to come from the Federal Government, primarily through NIH. In 1983, for example, 77 percent of health R&D funds used by universities came from the Federal Government; 19 percent from university, state, local, and other nonprofit sources; and 4 percent from industry. While industry has an important role in the continuum of health science research, its emphasis is chiefly on development and application. The primary search for basic knowledge will continue to be conducted by universities and Federal laboratories, with Federal dollars.

We are now entering the fifth decade of the Federal-academic partnership in biomedical research. We can take a degree of encouragement in making predictions for the remainder of the 1980's from the fact that the principles shaping the partnership have changed little since the years immediately after World War II. A number of issues we face in the 1980's were foreseen in the 1940's--for exam-

\*Keynote Address, Symposium on Genetics and Nutrition: Relevance to Learning Disabilities, San Francisco, California, February 20, 1985.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



ple, what to do about obsolescent equipment and instrumentation, patents, indirect costs, rising direct costs, and small business involvement. The Federal approach to support health research through universities has served the national interest well through the years. The basic concept of the Federal-academic partnership was expressed in a 1945 report entitled, "Science--The Endless Frontier," written by Dr. Vannevar Bush, the President's Science Advisor. The flavor and substance of the document stand up well when viewed from the perspective of nearly 40 years. Permit me to read a few sentences from it:

"The publicly and privately supported colleges, universities, and research institutes are the centers of basic research. They are the wellsprings of knowledge and understanding. As long as they are vigorous and healthy and their scientists are free to pursue the truth wherever it may lead, there will be a flow of new scientific knowledge. ...Progress in the war against disease results from discoveries in remote and unexpected fields of medicine and the underlying sciences."

Such "discoveries in remote and unexpected fields" are the objective of the Government-university partnership. A concept expressed in the 1920's by Alfred North Whitehead characterizes our present effort. Whitehead said: "The proper function of a university is the imaginative acquisition of knowledge." I like to think that this concept can be applied to the function of NIH as well.

An isolated fact is interesting but not useful until imagination places it in a larger context. At that point, as Whitehead said in the same lecture, "a fact is no longer a bare fact: it is invested with all its possibilities." To be engaged in "the imaginative acquisition of knowledge" at this time is, in my opinion, the most exciting opportunity in the history of health science research. The recent flood of advances in biomedical research has justifiably led to the use of the phrase "biological revolution" to describe the present state of the life sciences. This surge of new knowledge, the result of almost four decades of vigorous public support of biomedical research, has produced outstanding opportunities for progress and has created an unprecedented potential for the application of this knowledge to the improvement of health. The barriers are coming down; biomedical science has probed the innermost secrets of living processes at the cellular and molecular levels. Let me mention just two of these areas of high promise to be pursued in the immediate future:

First, the development of recombinant DNA technology has given us an exciting tool that allows us to transfer hereditary units from one species to another and permits bacteria to become factories for the production of substances of biological, agricultural, and medical importance. The use of this technique has already led to the synthetic production of human insulin, somatostatin and growth hormone. Recombinant DNA technology also can be used to produce large quantities of pure antigen which, in turn, can be used as vaccines for immunization against infectious agents.

Second, the past decade has seen rapid growth in our knowledge of neurobiology; we are achieving a progressively better understand-

ing of the function of the brain and central nervous system in health and disease. The discovery of slow viruses that cause significant neurological damage has been a major advance. Methods of opening the blood-brain barrier selectively have been identified and are being investigated to allow enzyme replacement in certain genetic diseases. Progress in microsurgery has greatly improved the outlook for patients with certain neurological conditions, including brain tumors and acoustic neuroma. New diagnostic tools, including computerized tomography (CT), positron emission transaxial tomography (PETT) and, most recently, nuclear magnetic resonance (NMR), allow detailed imaging of the living human brain and its functions, and promise to uncover a wealth of knowledge. Work on neurotransmitters, such as L-Dopa, and neuropeptides, such as enkephalins, has greatly expanded our knowledge of communication within the central nervous system. I agree with many scientists who believe that neurobiology is the frontier science of this decade.

Scientific advances such as these form the deepening foundation upon which we will build important achievements and health benefits in the years ahead. They will not come quickly or easily, but there is a momentum to science that will not be denied. There is much to do.

The rate of progress in the ceaseless war on disease is a function of scientific opportunity, which we now have in abundance, the imaginative insight of scientists, and available funds. We are simultaneously involved in the adventure of discovery for its own sake and in pursuit of better health for all. What a combination: satisfying work in a great humanitarian cause!

But how shall we make sure that the momentum of scientific discovery is continued? We have entered a period of financial constraint in biomedical science. The period of explosive growth of support for biomedical research of the fifties and sixties, when the NIH budget increased 20-fold in constant dollars in 13 years, is long over. The second stage rocket of the cancer, heart disease and stroke initiative has now played out. In my view, we are facing more than a temporary funding constraint in biomedical science; rather, we have entered a new steady state that, all of us, NIH and universities alike, would do well to view as the future norm. A number of painful adjustments will be necessary if we are to secure the greatest amount of the best science within our available resources. Since it may not be possible to continue all the efforts and programs we have come so passionately to cherish, we will have to set our research priorities carefully, taking into consideration a wide variety of factors: the overall mission of NIH to support research in pursuit of health, scientific considerations, and specific public mandates and assignments as expressed by Congress and the Administration.

The basis for development of the fiscal year 1986 budget for the NIH is the administration's policy essentially to freeze domestic programs at the 1985 funding level. To accomplish this purpose without upsetting the stability of our major research support program

requires adjustments in the FY 1985 appropriations, primarily in the funding of research grants.

Research project grants to individual investigators continue to receive the highest priority because they support the primary source from which fundamental discoveries emerge. Thus they represent the key mechanism in Federal support of biomedical research. The 1985 budget will fund 5,000 new and competing research project grants and approximately 12,172 noncompeting continuations of awards made in previous years. About 646 of the 5,000 new and competing awards will receive funding in 1985 for three years of support. This multiyear funding policy is intended to avoid significant fluctuations in the number of grants NIH is able to support and to lower future non-competing requirements.

The 1985 budget also includes \$482,144,000 for 500 research centers. This represents an increase of four centers over 1984 and includes support for three new research centers on Alzheimer's disease and related disorders. As with research project grants, some of the research centers will receive multiyear support. Approximately 45 of the 500 centers will be awarded two years of support from FY 1985 funds.

Turning now to the 1986 budget, the request for NIH is \$4,852,680,000, a decrease of \$282,048,000 from the comparable 1985 level. Examined from a program level perspective, however, the request represents close to a 2 percent increase over 1985. This increase reflects the 1986 budget authority, plus the second year resources provided from 1985 funds. The budget request will support 12,957 full-time equivalent staff positions, a reduction of 150 from the 1985 level of 13,107, and a reduction of 704 from the 1984 actual usage of 13,661.

The budget also assumes savings of \$29.8 million in administrative costs and \$19.1 million as a result of the proposed five percent reduction in pay costs.

The request supports an estimated 5,000 new and competing research project grants and 11,242 noncompeting research project grants. Including the estimated 646 grants which were multiyear funded in 1985, the total number of active research project grants in 1986 will be 16,888. Direct costs of research project grants in 1986 will be funded on the average at the historical level of 97 percent of costs recommended by study sections for new and competing awards, and 99 percent of committed amounts for noncompeting awards. The NIH aggregate average costs will be approximately 6.0 percent higher than 1985 for new and competing awards, and about 7.8 percent higher for noncompeting continuations.

The 1986 request includes \$412,391,000 to fund 455 research centers. The 45 centers that were multiyear funded in 1985 will remain active in 1986, thus a total of 500 centers will be ongoing in 1986, the same number as will be supported in 1985. The budget assumes the same average costs in 1986 as in 1985.



As part of the Administration's effort to hold domestic programs at the 1985 level, indirect costs associated with research grants will be held at the 1985 rate. It is estimated that this measure would save about \$23 million.

NIH will support approximately 9,891 research trainees in 1986; the same number is estimated to be supported in 1985. This represents about 94 percent of the level recommended by the National Academy of Sciences for the NIH. No increases are included in the request for stipend levels, tuition increases, or institutional costs.

Budget authority of \$561,653,000 is requested for intramural research in 1986. The decrease of \$17,638,000 from the 1985 level represents the savings resulting from the reduction in administrative costs and the 5 percent paycut.

In summary, the 1986 request for NIH represents a realistic level of Federal support for biomedical research and research training in the context of the rising Federal deficit and the need for Federal fiscal austerity. The request emphasizes support for basic research, providing support for 5,000 new and competing research project grants, and 11,242 noncompeting continuations at levels close to full study section recommendation and committed amounts. In other extramural funding mechanisms, the request supports ongoing programs at basically 1985 dollar levels. Overall, the 1986 request reflects the Administration's commitment even in times of scarce resources to a vigorous program of biomedical research and research training.

Whatever our priorities and programs, which may vary as conditions and opportunities warrant, there are certain abiding principles that will continue to guide our decisions.

One is that the pursuit of basic knowledge is the foundation of all progress in the health sciences. We must continue to increase our store of fundamental knowledge. Any relaxation of that necessarily long-term objective in favor of short-term advantage is a threat to the eventual triumph over disease and suffering.

A second fundamental principle is that investigator-initiated research into biological processes holds the greatest promise of significant discovery. Through competing research projects, we tap the best minds and most creative ideas, weigh them through peer review of substance and methodology, and test them through challenge and open exchange of information. We will continue to place top priority on the award of new and competing research project grants, and on the support of such projects for the life of the award period. Incidentally, in fiscal year 1984, which ended on September 30, we managed to fund 5,493 such new and competing renewal awards, plus several new research center awards.

Finally, the third element of these timeless principles is that there is a continuing need to assure a supply of well-trained scientists to carry out the research to meet national health goals. There is a close interrelationship between the continued productivity of research and the availability and replenishment of the supply of qualified investigators.

Beyond those statements of principles are certain other responsibilities that also must be considered by NIH. We must recognize a need for balance between the fundamental pursuits and other NIH program components in order to assure uninterrupted progress in all segments. Among those additional components are the following six:

- o Research centers which conduct multidisciplinary research focused on specific health problems, integrate basic research with clinical application, and provide a vehicle for transferring new scientific knowledge into practice in community health care settings.

- o Research resources to strengthen, enhance, and maintain the infrastructure of biomedical research, including instruments and facilities.

- o Biomedical communications involving the acquisition, storage, and dissemination of information needed in research, health professional education, and the delivery of health care services.

- o International research activities to facilitate the exchange of scientific information and promote collaborative research efforts.

- o Clinical trials to advance knowledge concerning the prevention, diagnosis, and treatment of disease and to provide evidence of safety and efficacy of new therapy.

- o Special emphasis on the prevention of disease and the promotion of health as part of a Department-wide initiative.

These, then, are the major responsibilities of NIH which must be weighed in establishing our priorities and programs for the future. But the underlying principles on which all of our work is built remain the pursuit of basic research, support of independent investigators and their ideas, and the training of future scientists.

For many years, the NIH has supported research in both genetics and nutrition, and their interaction. I can not think of a more important interaction that affects adaptation and thus development. In addressing the importance of genetics, I would like to quote the research recommendations from the book, Genetic Screening: Programs, Principles and Research, which Dr. Byrne just referred to. (The two persons responsible for the book are Dr. Simopoulos and Dr. Childs.)

- 1) "Research in genetic screening should be governed by the rigorous standards employed in laboratory investigations. Special efforts should be made to evaluate all aspects, even of routine

150

procedures, and the social and ethical ramifications of screening in the lives of the persons tested should be investigated. So far, experience in genetic screening is insufficient to foresee and to forestall all possible untoward side effects. Accordingly, it should be approached in an experimental mood. At present, it is impressions that prevail, rather than data collected and analyzed according to scientific rules."

2) "It is important that screening be used to study the natural history of genetic disorders for which there is no treatment at this time. Such research in which the object of screening is to discover the full range of expression of the disease, will further the development of new methods of treatment and can provide the control data needed to evaluate proposed treatments. Particular effort must be exerted to protect individuals identified by such screening against the psychological and social hazards that attend all screening programs but whose impact may be enhanced by the lack of an effective treatment. "

3) "Research should be supported in adapting discoveries of new genetic characteristics for screening purposes. This research includes increasing the number and quality of tests, reducing their cost, building regional networks of laboratories and other facilities to broaden and improve service, and designing simple, inexpensive, and effective treatments for newly discovered diseases. The acquisition of genetic knowledge is proceeding exponentially and much of it is germane to the aims of genetic screening."

4) "Research to discover polymorphic alleles occurring in high frequency should receive more substantial support. Certain common alleles have been shown to be associated with disease, and it is predictable that many more will also be implicated."

Although stated approximately 10 years ago, these research recommendations are still pertinent today.

As many of us know, genetic endowment provides the potential for development, but full expression requires the presence of an optimal environment. For maturation and growth to be maintained, there must be an adequate provision of nutrients. Available substrate from the diet is important in modifying the developmental pattern of various enzymes. Biochemical genetics has advanced our understanding of the interactions between heredity and nutrition, of the development and treatment of certain diseases, and of normal development and disease prevention. Research on genetics and nutrition, supported by the NIH includes studies on inborn errors of metabolism; metabolic differences in nutritional requirements; chromosomal aberrations and determinations of cellular function, especially DNA repair mechanisms; and the effects of dietary intervention on inherited diseases or conditions. In FY 1982, NIH expenditures for research in this area totaled \$19 million or 13 percent of the total nutrition expenditures, whereas in FY 1983 expenditures were \$28 million or 17 percent of total nutrition expenditures.



I would like to spend the remaining time to present some of the highlights of this research. The study of genetic variants in man and in animal models helps to advance our understanding of both normal and abnormal biochemistry. The various inborn errors of metabolism under investigation include phenylketonuria, galactosemia, maple syrup urine disease, urea cycle enzyme deficiencies (e.g. isovaleric acidemia, hyperglycinemia, hyperargininemia, citrullinemia, methylmalonic aciduria, hyperornithemia, hyperlysinemia) biotin responsive carboxylase deficiency, cystinosis, and Menkes' kinky hair syndrome, among others.

Various dietary manipulations can overcome or bypass the enzymatic defects that characterize the inborn errors of metabolism. For example, elimination diets can prevent the accumulation of nutrient substrates in metabolic pathways prior to the enzymatic defect. Galactose is eliminated from the diets of persons with galactosemia, branched chain amino acids from those with maple syrup urine disease, phenylalanine from those with phenylketonuria, and nonessential amino acids from those with urea cycle enzymopathies.

Research on genetic-nutrient interactions in animal models aims to establish possible interactions of mutant and inbred animals with trace elements; to elucidate their mechanism of action; and to investigate the interaction of nutrients, genes and drugs.

Analysis of the influence of combined genetic and nutritional factors on drug teratogenicity continues to improve our understanding of the interactions between genetic and nutritional factors in mammalian development. For example, high levels of dietary zinc may ameliorate the deleterious effects of 6-mercaptopurine on embryonic DNA metabolism and maternal toxicity. In addition, increasing levels of dietary zinc in the CBA mouse reduces acetazolamide induced fetal malformations. This teratogen inhibits carbonic anhydrase by binding to the zinc ion at the enzyme's active site. The interaction between zinc and acetazolamide appears to be influenced by genetic background.

Research on the nonnutrient components of food, i.e., the intentional additives and the accidental chemical contaminants, explores the various facets of adverse biological effects associated with long-term low level exposure. Metabolic functions, interactions with cellular macromolecules, and the mechanisms of toxic action are examined in order to assess mutagenicity and carcinogenicity risks of toxic substances in food.

Studies on the behavioral effects of malnutrition have historically been a great interest of the National Institute of Child Health and Human Development (NICHD). In early studies it was learned that a substantial proportion of the apparent behavioral sequelae of early malnutrition can be ascribed to the impoverished economic and social environments in which malnutrition flourishes.

Scientists are working with four different rat models in order to separate nutritional from environmental variables. This group has

found that malnourished rat pups (mother-deprived, reared by non-lactating aunt) are slower than controls to habituate to open field testing. These investigators have also noted that environmental factors such as handling, can produce behavioral effects as strong as those of undernutrition. Also, environmental variables could remediate the usual behavioral deficits produced by malnutrition while having little effect on the deficits in brain size and composition. This study indicates that malnourished rats benefit less from environmental enrichment than normal animals.

One of the primary concerns of research on malnutrition has been to use measures of behavioral change which are both sensitive enough to detect possible effects of malnutrition and simple enough to be interpreted unambiguously. The former concern arose because the behavioral effects of malnutrition have seemed minor compared with brain deficits. The latter concern arose because many behavioral measures of higher function such as learning, have not been clearly interpretable.

Studies on the role of nutrition in central nervous system development include research on early brain development. Some studies are examining the hypothesis that several pathways of brain metabolism in the developing animal are linked to nutrient availability in the brain. Such studies attempt to quantitate developmental changes of both blood-brain transport and brain metabolism of amino acids. This research will increase our knowledge as to whether such compounds as choline, ornithine, and adenosine are essential to the developing brain and provide the necessary rationale for monitoring plasma levels of such nutrients in the fetus.

Additional studies examine undernutrition and its effect on the plasma membranes of synaptic nerves in the brain. Investigations have demonstrated that offspring of undernourished rats have a decreased concentration of protein and changes in the synthesis of gangliosides, glycoproteins, and other specific proteins in the synaptic plasma membranes. This decrease in protein concentration may precipitate the synaptic abnormalities observed in these animals.

Other investigations on the effect of diet on brain neurons, particularly the synthesis and release of serotonin by brain neurons have examined the effects on the sleep patterns of newborn infants of variations in diet designed to affect tryptophan availability. It is known that the synthesis and release of serotonin by brain neurons is proportional to the availability in the brain of its precursor, tryptophan. The brain tryptophan concentration is influenced by dietary intake of tryptophan and other large neutral amino acids (valine, leucine, isoleucine, tyrosine, methionine, and phenylalanine) that compete with tryptophan for transport across the blood brain barrier, as well as the intake of carbohydrate and associated insulin secretion.

A program project is designed to assess the behavioral effects of lead exposure from dietary, maternal and air-borne sources.

Included among the projects are studies of neuropsychological performances of school children with high and low levels of dentine lead. Multiple logistic regression analysis indicates that an elevated dentine lead level increases a child's risk of needing daily remedial academic aid ( $p=.052$ ). Half of the children above the 90th percentile of the lead distribution were receiving remedial aid, versus 16.9% of the children below the 90th percentile. On many outcome measures (e.g., Otis-Lennon IQ, Myklebust total and subscale scores), the children's scores were dose-related to lead grouping; the poorest performances were associated with higher levels of lead.

Children with elevated levels of dentine lead (20 parts per million) achieve IQ scores (WISC-R) which are below those expected based on knowledge of their mothers' IQ. The amount by which a child's IQ fell short of the expected value increased with increasing levels of dentine lead. At doses experienced by approximately 10% of urban American school children, lead appears to disrupt the association between maternal and child intelligence.

I would like to add that recently the Centers for Disease Control lowered the levels of lead considered poisonous to 35 micrograms per deciliter, down from the 1978 guideline of 50 micrograms per deciliter. New studies demonstrate that little or no margin of safety is associated with the previous threshold.

Alcohol consumption affects health, and at no other time is the effect of alcohol consumption more dramatic than during fetal development. In order to better understand the effect of alcohol consumption during pregnancy on the proper development of the fetus, an animal model of pigtailed macaques has been developed to determine the levels of binge alcohol consumption that can produce defects in infants of mothers who drink during pregnancy. Early results of research using this animal model indicate that six cocktails consumed once a week by the mothers may cause serious problems in newborns. Research in this area is examining a number of factors including the time when drinking during pregnancy causes the most damage. Studies suggest that brain development can be severely altered by fetal exposure to alcohol even beyond the first trimester.

From time to time the NIH identifies areas for further research and brings them to the attention of the scientific community through program announcements (PA's), requests for applications (RFA's), and requests for proposals (RFP's). In FY 1983, the NICHD published one PA and one RFP that focused on some aspect of genetics and nutrition.

The PA, "Behavioral/Biomedical Interdisciplinary Research Training," encouraged applications for National Research Service Awards (NRSA) for both individual postdoctoral fellowships and institutional training grants for pre and postdoctoral trainees in order to support individuals for research in the interdisciplinary area of behavior and biomedicine. In order to understand the complex interactions between basic biological mechanisms underlying development and the behavioral determinants of development, applications for interdisciplinary research training are encouraged in the areas of



behavior and nutrition, developmental genetics, behavioral pediatrics, developmental behavioral pharmacology, and developmental behavioral biology. In the area of behavior and nutrition, studies are encouraged on the failure to thrive in infants, obesity, learning deficits, hyperactivity, anorexia, control of appetite and satiety, and nutritional factors in brain/behavioral development.

The RFP entitled "Successive Small-For-Gestational Age Births: A Longitudinal Study of Fetal Growth and Perinatal Outcome," sought proposals for a longitudinal prospective study of fetal growth and perinatal outcome of women at risk of delivering small-for-gestational-age births (defined as birth weight less than the 10th percentile for gestational age). The study is to identify at risk mothers for intrauterine growth retardation using ultrasound during the second and early third trimesters of pregnancy, to collect interview and prenatal medical data, to distinguish the two primary types of fetal growth retardation at birth, to evaluate postnatal growth during the first year of life in order to detect either catch-up accelerated growth or continued slow growth, and to assess the known risk factors (maternal smoking, underweight of malnourished mothers and hypertension or other medical factors) and any newly identified risk factors using a geographically-based population of pregnant women. Specific nutrition factors to be ascertained from 1,500 expectant mothers in their second and third trimesters of pregnancy include: dietary habits before becoming pregnant; a 24-hour log of dietary intake taken at three times during the second and third trimesters; fat deposition at three time intervals during the second and third trimesters; and metabolic tests including an oral glucose tolerance test obtained in the second trimester.

In addition, research on learning disabilities is being encouraged at the NIH by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) which jointly with NICHD issued a program announcement seeking proposals in the area of brain dysfunction in disorders of learning. NINCDS also issued jointly with the National Institute of Mental Health (NIMH) a request for applications for the establishment of multidisciplinary research centers for the study of the neurological basis of disorders of language, behavior and learning during infancy and early childhood. In FY 1984 the NINCDS funded 4 projects for a total of \$427,000.

Intramural research efforts of NINCDS in this area include two large-scale longitudinal studies from the Collaborative Perinatal Project. In one monograph, the symptoms and antecedents of minimal brain dysfunction are analyzed. In a second, the development and environment of low achieving children of normal intelligence is investigated, beginning in the prenatal period.

In the immediate future, NINCDS plans to continue its collaboration with NICHD in program development for the support of research on the etiology and subtyping of specific learning disabilities.

In addition, the NIH is represented on the Interagency Task Force on Learning Disabilities and Attention Deficit Disorders

15  
chaired by Dr. Larry Silver, Deputy Director of NIMH. The purpose of this group, established at the request of the House Appropriation's Committee, is to develop effective research strategies related to these disorders and disabilities.

In closing, I would again like to quote from the book, Genetic Screening: Programs, Principles and Research on the relationship of genetics to preventive medicine:

"Should increased emphasis on prevention of disease and the promotion of good health ever become more than a pious hope, then analysis of each individual genotype will be an essential prelude to guidance toward and away from particular conditions known to enhance or to threaten the individual's adaptive state. Such an approach is somewhat at variance with current preventive medicine in which rules of avoidance or moderation are recommended for everyone. The genetic view, which predicts that not everyone is equally susceptible to all threats, suggests that nonsusceptibles should be spared the fearful anticipation of events that never materialize and the onerous requirement to abide by rules that are, for them, irrelevant."

This statement, although made 10 years ago, is still pertinent, and is consistent with the objectives and rationale of today's symposium.

ADDRESS\*

BY

JAMES B. WYNGAARDEN, M.D.\*\*

I FEEL MYSELF VERY FORTUNATE TO HAVE BEEN INVITED TO PARTICIPATE IN THIS AWARDS DINNER AND TO JOIN WITH THIS DISTINGUISHED GATHERING IN EXPRESSING WARMEST CONGRATULATIONS TO THE YOUNG MEN AND WOMEN WHO CONSTITUTE THE TOP FORTY OF THE 1985 HONORS GROUP SELECTED IN THE COURSE OF THE 44TH ANNUAL SCIENCE TALENT SEARCH.

THE WESTINGHOUSE ELECTRIC CORPORATION AND THE WESTINGHOUSE EDUCATIONAL FOUNDATION ARE ALSO TO BE CONGRATULATED AND THANKED. THEIR FINANCING OF THE ANNUAL SCIENCE TALENT SEARCH IS A NOTABLE CONTRIBUTION TO THE ADVANCEMENT OF SCIENCE IN AMERICA. FURTHERMORE, THE ADMINISTRATION OF THIS PIONEERING ENDEAVOR BY SCIENCE SERVICE IS A SIGNIFICANT FACET OF ITS ACTIVE ROLE IN INTERPRETING AND PROMOTING PUBLIC UNDERSTANDING OF SCIENCE.

THESE ANNUAL AWARD DINNERS CONSISTENTLY HAVE BEEN ATTENDED BY THE MEN AND WOMEN WHO CONSTITUTE MUCH OF THE SCIENTIFIC COMMUNITY OF OUR NATION'S CAPITAL, AND EACH IS ESPECIALLY EXCITING BECAUSE OF THE PRESENCE OF THE YOUTHFUL SCIENTISTS. MOST OF WHAT I WILL HAVE TO SAY WILL EITHER BE ABOUT THEM OR DIRECTED PARTICULARLY TO THEM. THEY ARE

---

\*PRESENTED AT THE 44TH ANNUAL SCIENCE TALENT SEARCH BY WESTINGHOUSE EDUCATIONAL FOUNDATION, WASHINGTON, D. C., MARCH 4, 1985.

\*\*DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND.



HERE, OF COURSE, BECAUSE OF THEIR SUCCESS THROUGH SEVERAL STEPS OF COMPETITION, BUT I TRUST THAT NONE WAS AS HARROWING AS AN EPISODE RELATED BY FRANK PRESS.

HIS STORY GOES THAT THERE WERE TWO YOUNG MEN HIKING IN ONE OF THE MORE REMOTE SECTIONS OF GLACIER NATIONAL PARK ONE AUGUST. AS THEY WENT AROUND A BEND IN THE TRAIL, THEY SPIED A LARGE BEAR IN THE DISTANCE, WHICH AT THE SAME INSTANT CAUGHT SIGHT OF THE HIKERS AND BEGAN LUMBERING EVER FASTER TOWARD THEM. THE TWO YOUNG MEN, ELBOWING EACH OTHER ON THE NARROW TRAIL, TURNED AND RAN HELTER-SKELTER AWAY FROM THE APPROACHING BEAR. ABOUT A QUARTER MILE DOWN THE TRAIL, THEY CAME UPON THEIR BASE CAMP WHERE THEY HAD LEFT THEIR TENT PITCHED WITH THEIR BELONGINGS STASHED INSIDE. ONE OF THE YOUNG MEN SCRAMBLED INTO THE TENT TEARING OFF HIS HIKING BOOTS AND HURRIEDLY TYING ON HIS RUNNING SHOES. THE OTHER YOUNG MAN, WHO WAS ANXIOUSLY--AND IN VAIN--LOOKING FOR A TREE TO CLIMB, ASKED THE OTHER, "WHY ARE YOU PUTTING ON YOUR RUNNING SHOES? DON'T YOU KNOW A MAN CAN'T OUTFRAN A HUNGRY BEAR?" THE YOUNG MAN WEARING THE RUNNING SHOES LOOKED AT HIS COMPANION AND SAID, "MAYBE SO, BUT I DON'T NEED TO OUTFRAN THE BEAR--I JUST NEED TO OUTFRAN YOU."

ALTHOUGH OUR HONOREES ARE HERE BECAUSE THEY COMPETED SUCCESSFULLY, AND, IN EVERY SENSE, ARE WINNERS, THIS IS NO ORDINARY COMPETITION. OLYMPIC GOLD, SILVER, AND BRONZE MEDALS ARE CONFERRED AFTER THE RACE, BUT THE WESTINGHOUSE AWARDS GO TO THE MOST PROMISING RUNNERS WHEN THEY

ARE STILL IN THE STARTING BLOCKS. IT DOESN'T DETRACT FROM THE HONORS BESTOWED TO OBSERVE THAT THE SELECTIONS ARE MORE IN THE NATURE OF CAREFUL WAGERS THAN APPRAISALS OF PERFORMANCE. TONIGHT'S DINNER IS MORE A CELEBRATION OF PROMISING BEGINNINGS THAN OF SUCCESSFUL CONCLUSIONS. IT IS ALSO THE KIND OF AN OCCASION THAT REMINDS MANY OF US OF OUR OWN YOUTH. FOR A TIME WE CAN RECALL AND SHARE WITH THE MEMBERS OF THE 1985 HONORS GROUP THE EXCITEMENT THAT COMES FROM FEELING THE STRONG ATTRACTION OF A SCIENTIFIC OR TECHNICAL DISCIPLINE--AND THE IMPATIENCE TO EXPLORE FOR OURSELVES ITS KNOWN AND UNKNOWN PARTS. IN ABSENCE OF THAT ZEST, NATURAL ABILITIES OR TALENTS COUNT FOR LITTLE. CERTAINLY THE INDIVIDUAL ACHIEVEMENTS THAT LED TO THE SELECTION OF OUR HONOREES TONIGHT ARE EXAMPLES OF THE APPLICATION OF THEIR TALENTS, BUT THE FORCE THAT MADE THE CRUCIAL DIFFERENCE--THE DRIVING FORCE--WAS THEIR FASCINATION WITH THE PROBLEMS THEY ADDRESSED. I SUSPECT THAT IN MANY CASES THIS DRIVING FORCE WAS REINFORCED BY THE PARENTS OF OUR HONOREES--PARENTS WHO JUSTIFIABLY CAN TAKE PRIDE IN THE RESULTS OF THEIR ENCOURAGEMENT AND NURTURE.

IT IS ALSO ENTIRELY APPROPRIATE THAT RECOGNITION IS GIVEN BY WESTINGHOUSE TO THE SCHOOLS FROM WHICH OUR HONOREES CAME. IN MY VIEW, HOWEVER, THE PLAQUES AWARDED TO THE SCHOOLS WERE EARNED NOT SO MUCH BY THE RIGOR AND THOROUGHNESS OF INSTRUCTION AS THE INSPIRED TEACHING THAT AWAKENED AND SUSTAINED THE INTEREST OF THE YOUNG STUDENTS IN BECOMING EXPLORERS OF THE REALM OF SCIENCE.

AS ONE WHO HAS SPENT THE MAJOR PORTION OF HIS PROFESSIONAL CAREER AS A UNIVERSITY FACULTY MEMBER, I HAVE SPECIAL ADMIRATION FOR THE ABILITY OF THE TEACHERS AT THE ELEMENTARY AND SECONDARY LEVEL WHO SO OFTEN INITIATE THE WONDERFUL PROCESS THAT LEADS STUDENTS THROUGH BRIGHT POTENTIAL TO SIGNIFICANT ACCOMPLISHMENT. IT IS THE KIND OF TEACHING SUGGESTED IN A RICH FRAGMENT FROM SPOON RIVER ANTHOLOGY ABOUT FATHER MALLOY OF WHOM IT WAS TOLD, "YOU WERE LIKE A TRAVELER WHO BRINGS A LITTLE BOX OF SAND FROM THE WASTES OF SAND ABOUT THE PYRAMIDS AND MAKE THEM REAL AND EGYPT REAL." INSPIRED TEACHING IN THE HOME OR IN THE SCHOOL WAS THE SUBJECT OF A TRENCANT COMMENT BY JACQUES BARZUN WHO SAID THE PURPOSE OF TEACHING IS TO "SET THE SPARK--AND THE STUDENT WILL TAKE FIRE WHERE HE (OR SHE) IS INFLAMMABLE."

THE IMPORTANCE OF SUCH INTELLECTUAL IGNITION CANNOT BE OVER-ESTIMATED. IN AN ESSAY ON "THE RHYTHM OF EDUCATION," ALFRED NORTH WHITEHEAD POINTED OUT THAT EDUCATION MUST ESSENTIALLY BE A SETTING IN ORDER OF A FERMENT ALREADY STIRRING IN THE MIND. HE REPHRASED HEGEL'S THREE STEPS OF PROGRESS OR GROWTH AND APPLIED THE ANALYSIS TO EDUCATION. THE FIRST STEP HE CALLED THE STAGE OF ROMANCE--A TIME WHEN STUDENTS FLIRT WITH IDEAS, WHEN, FOR EXAMPLE, THEY FIND THEMSELVES ATTRACTED, FOR NO LOGICAL REASON, FIRST TO ONE AND THEN TO ANOTHER FACET OF SCIENCE--OR TO ANOTHER AREA ENTIRELY. WHITEHEAD CALLS IT A TIME WHEN "THE SUBJECT MATTER HAS THE VIVIDNESS OF NOVELTY; IT HOLDS WITHIN ITSELF UNEXPLORED CONNECTIONS WITH POSSIBILITIES HALF-DESCRIBED BY GLIMPSES AND HALF-CONCEALED BY THE WEALTH OF MATERIAL. IN THIS STAGE, KNOWLEDGE IS NOT DOMINATED BY SYSTEMATIC PROCEDURES." THAT WILL COME LATER.



WHITEHEAD CALLED THE SECOND STEP THE STAGE OF PRECISION. IT IS A TIME OF DISCIPLINE WHERE THE EXTENT OF RELATIONSHIPS IS SECONDARY AND EXACTNESS OF FORMULATION IS PRIMARY. WHITEHEAD SAID THAT THIS STAGE IS "THE STAGE OF GRAMMAR, THE GRAMMAR OF LANGUAGE AND THE GRAMMAR OF SCIENCE." HE ALSO COMMENTED THAT "A STAGE OF PRECISION IS BARREN WITHOUT A PREVIOUS STAGE OF ROMANCE; UNLESS THESE ARE FACTS WHICH HAVE ALREADY BEEN VAGUELY APPREHENDED IN THEIR BROAD GENERALITY."

THE FINAL STEP WAS CALLED THE SYNTHESIS BY HEGEL, AND BY WHITEHEAD, THE STAGE OF GENERALIZATION. WHATEVER--IT IS THE FRUITION--THE GOAL OF PRECISE TRAINING. THE TIME WHEN THE AFFECTION FOR AN IDEA HAS MATURED, HAS BEEN DISCIPLINED, AND BECOMES A POWERFUL TOOL FOR ACCOMPLISHMENT.

I DON'T WISH TO BELABOR THIS DESCRIPTION OF THE STRUCTURE OF INTELLECTUAL GROWTH, BUT IT PROVIDES A USEFUL FRAMEWORK IN WHICH TO PLACE SOME THOUGHTS I WISH TO CONVEY. LOOKING AT EDUCATION IN THIS WAY MAKES US REMEMBER HOW IMPORTANT IT IS FOR US ALL TO HAVE A PERIOD IN OUR LIVES WHEN WE CAN DREAM ABOUT CAREERS--WHEN WE CAN ROMANCE IDEAS. IT IS ALSO A REMINDER TO ALL CONCERNED OF THE NECESSITY OF EXPOSING YOUNG PEOPLE TO A WIDE RANGE OF POSSIBILITIES. THERE IS ABSOLUTELY NO WAY TO MAKE A CHOICE THAT ONE DOES NOT KNOW ABOUT.

EARLIER, I SAID THAT I WOULD ADDRESS SOME THOUGHTS EXCLUSIVELY TO THE HONOREES. HERE IS ONE--

EACH OF YOU HAS ALREADY TASTED AN UNUSUAL DEGREE OF SUCCESS IN A PARTICULAR AREA--AND IN THAT SENSE YOU HAVE PROCEEDED RAPIDLY THROUGH ONE FULL CYCLE OF LEARNING--BUT IT WOULD BE UNFORTUNATE INDEED IF YOU WERE TO SETTLE DOWN TO AN EXCLUSIVE RELATIONSHIP WITH THE SUBJECT OF YOUR FIRST SUCCESS. YOU HAVE PROVED YOUR RECEPTIVENESS TO IDEAS AND, OF ALL TIMES IN YOUR LIFE, IT IS NOW THAT YOU ARE IN A POSITION TO ROMANCE OTHER IDEAS. IT IS A TIME WHEN YOU OWE IT TO YOURSELF TO FORCE YOUR ATTENTION TO STRAY A BIT.

ALL TOO OFTEN ONE SEES SCIENTISTS PLODDING THROUGH WHAT SHOULD BE THEIR MOST PRODUCTIVE YEARS ADDING SMALL AND PITIFUL ORNAMENTS TO THE THEME THEY PURSUED TO A DOCTORATE 10 TO 20 YEARS AGO.

FOR A NUMBER OF REASONS, IT IS NOT EASY TO ENTER A NEW CYCLE OF LEARNING. IT TAKES A STRONG SENSE OF SELF WORTH AND COURAGE AND SECURITY TO FOLLOW A NEW PASSION IN SCIENCE, PARTICULARLY IF ONE HAS ALREADY ENJOYED A DEGREE OF SUCCESS IN ANOTHER.

A PRACTICAL FACTOR THAT WORKS CURRENTLY TO LIMIT THE FLEXIBILITY OF AN ESTABLISHED INVESTIGATOR IS THE KEEN COMPETITION FOR SUPPORT. WHEN SCIENTISTS WHO HAVE ACHIEVED RECOGNITION IN A PARTICULAR FIELD SEEK TO PURSUE STUDIES IN ANOTHER AREA, THEY ARE AT A CONSIDERABLE DISADVANTAGE WHEN COMPETING IN AN ARENA WHERE THEIR RECORD OF ACCOMPLISHMENT IS NOT KNOWN, NO MATTER WHAT ABILITIES OR SCIENTIFIC INSIGHTS THEY MAY HAVE TO OFFER. THIS IS A DIFFICULT PROBLEM WE ARE STUDYING AT THE NATIONAL INSTITUTES OF HEALTH IN AN ATTEMPT TO DEVISE PRACTICAL

MEANS FOR SUPPORTING RECOGNIZED SCIENTISTS WHO WISH TO SWITCH TO NEW AREAS OF RESEARCH AFTER HAVING CONTRIBUTED GREATLY IN OTHER AREAS.

I MAKE THIS POINT TO EMPHASIZE TO YOU THE VALUE OF THE RELATIVE FREEDOM OF CHOICE YOU NOW ENJOY, A FREEDOM THAT UNFORTUNATELY WILL BE NARROWED PROGRESSIVELY IN THE COURSE OF YOUR CAREER. AND SO I ENCOURAGE YOU NOT TO BE CONCERNED IF AREAS OF LEARNING OTHER THAN SCIENCE OR DISCIPLINES IN SCIENCE OTHER THAN THE ONE THAT BROUGHT YOU THIS YEAR TO WASHINGTON ARE BEGINNING TO APPEAL TO YOU AND EVEN IF THEY SHOULD CAPTURE YOU. I CAN VISUALIZE THE LASTING BENEFITS FOR SOCIETY THAT COULD RESULT IF ONE OR MORE OF YOU SHOULD DECIDE TO APPLY YOUR INSIGHTS AND DRIVE TO A CAREER IN PUBLIC SERVICE AS, FOR EXAMPLE, A MEMBER OF CONGRESS. FOR YOUNG PEOPLE AS TALENTED AS YOU WILL LIKELY DO BEST THAT IN WHICH THEY ARE THE MOST INTERESTED. AND FURTHER, BECAUSE THE RANGE OF YOUR INTERESTS IS A DETERMINANT OF YOUR RANGE OF ACCOMPLISHMENT, IT IS IMPERATIVE THAT YOU BE RECEPTIVE.

AN UNUSUAL DEFINITION OF EDUCATION WAS SUGGESTED SOME YEARS AGO. IT GOES LIKE THIS--NO MATTER HOW WELL TRAINED ONE MIGHT BE, THE DEFINITION STATES THAT A PERSON IS NOT EDUCATED IF HE OR SHE CANNOT ANSWER "YES" TO EACH OF THREE SPECIFIED QUESTIONS.

THE FIRST QUESTION--CAN YOU ENTERTAIN AN IDEA; THAT IS, DO YOU HAVE THE OPENNESS OF MIND, THE OBJECTIVITY OF OUTLOOK, THE CONCERN FOR TRUTH WHICH WOULD ENABLE YOU TO ENTERTAIN EVERY IDEA PRESENTED TO YOU ON ITS MERIT--NOT ACCEPTING OR REJECTING A NEW IDEA BECAUSE IT HAPPENS



TO BE FASHIONABLE? THIS RECEPTIVENESS TO IDEAS IS THEREFORE THE CRUCIAL QUESTION IN THE REALM OF INTELLECTUAL EDUCATION, AND CERTAINLY IN SCIENCE.

THE SECOND QUESTION--CAN YOU ENTERTAIN OTHERS? (THIS DOESN'T MEAN TO PERFORM AS AN ENTERTAINER.) BUT IT ASKS, CAN YOU EXPAND THE FRONTIERS OF YOUR EGO SO AS TO INCLUDE OTHER HUMAN BEINGS IN THE SWEEP OF YOUR SYMPATHY AND UNDERSTANDING? HAVE YOU THE WILLINGNESS AND CAPACITY TO SHARE THE JOYS AND SORROWS OF OTHERS? AND OF SPECIAL SIGNIFICANCE TO THOSE WHO PURSUE PROFESSIONAL CAREERS--CAN YOU ENTERTAIN THE IDEAS OF OTHERS? UNWILLINGNESS TO LISTEN TO CRITICISM OR SUGGESTION IS A DANGEROUS, EVEN SELF-DESTRUCTIVE, TRAIT FOR A SCIENTIST OR ENGINEER. IT IS SAID THAT CONFUCIUS ONCE WAS ASKED WHY HE REFERRED TO ONE OF HIS DISCIPLES AS "CULTURED." HIS ANSWER -- "HE IS QUICK AND FOND OF LEARNING AND NOT ASHAMED TO ASK OF THOSE BENEATH HIM. THAT IS WHY HE IS CALLED CULTURED."

THE THIRD QUESTION--CAN YOU ENTERTAIN YOURSELF; THAT IS, HAVE YOU ANY INNER RESERVES TO FALL BACK UPON WHICH WILL ENABLE YOU TO ENJOY YOUR OWN COMPANY--OR MUST YOU BE RUSHING FROM ONE THING TO ANOTHER WHETHER IN THE WAY OF SO-CALLED WORK OR SO-CALLED AMUSEMENTS IN ORDER TO AVOID THE BOREDOM OF YOUR OWN COMPANY?

YOU ARE PROBABLY FAMILIAR WITH THE STORY OF THE MAN WHO WENT TO A PSYCHIATRIST BECAUSE HE TALKED TO HIMSELF. THE DOCTOR ASSURED THAT THIS BEHAVIOR IS NOT UNUSUAL AND THAT HE SHOULDN'T WORRY ABOUT IT. "BUT," THE MAN PROTESTED, "DOCTOR, I'M SUCH A FRIGHTFUL BORE."

PERMIT ME TO RETURN BRIEFLY TO THE SECOND QUESTION--CAN YOU ENTERTAIN OTHERS?--BECAUSE IT HAS SPECIAL RELEVANCE TO TODAY'S SCIENCE.

AT ONE TIME, THE SCIENTIST COULD BE PRODUCTIVE WORKING ALONE--AND THAT WAS THE USUAL PATTERN. UNDER TODAY'S CONDITIONS, HOWEVER, A TEAM EFFORT IS THE RULE. EFFECTIVENESS OF THE SCIENTIFIC EFFORT UNDER THESE CONDITIONS IS INFLUENCED BY SUBJECTIVE QUALITIES AND INTERESTS OF THE INDIVIDUALS WHO MAKE UP THE PARTNERSHIP AND ESPECIALLY BY MATTERS AS SIMPLE AS HOW THEY GET ALONG WITH EACH OTHER.

LITERACY, IN THE FULLEST SENSE OF THE WORD, IS AN ABSOLUTE ESSENTIAL FOR TODAY'S SCIENTIST OR ENGINEER. IT IS EASY TO FORGET THE TRUISM THAT RESEARCH HAS NOT BEEN COMPLETED UNTIL IT HAS BEEN REPORTED. A CRITICAL TASK OF THE SCIENTIST IS TO PRESENT--TO PUBLISH--THE RESULTS OF HIS OR HER RESEARCH FULLY, HONESTLY, AND--ONE WOULD HOPE--CLEARLY.

FURTHERMORE, THE ABILITY TO DESCRIBE A CONCEPT ACCURATELY, ECONOMICALLY, AND PERSUASIVELY IS AN ESSENTIAL SKILL FOR THE RESEARCHER WHO SEEKS GRANT SUPPORT AT A TIME WHEN THERE ARE MANY MORE GOOD IDEAS FOR STUDIES THAN FUNDS TO SUPPORT THEM.

PERHAPS THE GOAL TO STRIVE FOR WAS DESCRIBED BY A BRITISH COLLEAGUE OF MINE WHEN HE SUGGESTED THAT MY CONTRIBUTION TO A BOOK HE IS EDITING SHOULD BE WRITTEN IN A "LEARNED BUT LUCID STYLE."

THIS LEADS ME TO ANOTHER BIT OF BRITISH ADVICE THAT I CAN AND WILL FOLLOW -- LORD BRABAZON OBSERVED " . . . THAT IF YOU CANNOT SAY WHAT YOU HAVE TO SAY IN 20 MINUTES, YOU SHOULD GO AWAY AND WRITE A BOOK ABOUT IT."

IT HAS BEEN AN HONOR AND PLEASURE TO BE WITH YOU TONIGHT AND TO EXTEND MY HEARTIEST CONGRATULATIONS.



ADDRESS\*

by

JAMES B. WYNGAARDEN, M.D.\*\*

I am very happy to be here today to help in dedicating the Science Research Institute Building in commemoration of Dr. Dolphus E. Milligan. As you may know, Dr. Milligan did much of his state-of-the-art, prize-winning research at laboratories of the National Bureau of Standards, which might be considered the counterpart of the National Institutes of Health (NIH) in the physical sciences. The Bureau of Standards, incidentally, is now located just several miles up the road from NIH in suburban Maryland.

I see this new building, devoted to pursuit of knowledge in all the sciences, as neither a beginning nor an endpoint but simply part of a continuum in our movement toward excellence. I am aware of the commitment to excellence by Morehead School of Medicine, and the alignment of the six fine institutions under the Atlanta University Center--especially the closer physical ties through this new science building--will serve to build on that foundation.

It seems especially fitting at this juncture in the evolution of the sciences that you intend to bring all the scientific disciplines together under one roof. For a time, the various branches of medical science seemed to move further and further apart as research became more specialized. But our reductionist approach--that is, our attempts to examine and explain the smallest details of details--has more recently begun to draw the various scientific disciplines back together. We seem to be experiencing a confluence of the many discrete and previously unrelated medical science subjects into a single, unified discipline. As Arthur Kornberg, of Stanford, has pointed out, "Anatomy, physiology, biochemistry, microbiology, immunology and genetics have now merged and are expressed in the common language of chemistry. In reducing structures and systems to molecular terms, all aspects of body form and function are beginning to blend into a logical framework."<sup>1</sup>

It seems that something similar is occurring across the sciences—for example, study of fluid turbulence by physicists may have impact upon work on drifting continents or galaxies or upon questions relating to blood clotting in artificial organs. Physicists in laser science may solve problems relating to lightwave communications, clinical surgery or diagnostics, or to separating uranium isotopes. It may well be that proximity here in the new science research building through formal meetings and seminars or through informal hallway encounters among faculty and students, may lead to totally unexpected insights and advances.

---

\*Keynote address given at the dedication of the Science Research Institute Facility at Atlanta University, Atlanta, Georgia, March 9, 1985.

\*\*Director, National Institutes of Health, Bethesda, Maryland

2

It is especially noteworthy that this occasion has brought together all the partners of the U.S. research enterprise--government, the private sector, especially industrial concerns, and of course, academia. Those responsible for drawing together industry and government to support this science endeavor are to be commended for their farsightedness. Back in 1976, the Science Research Institute attracted the support of the National Science Foundation for a computer resource and then, in 1972, was awarded major support from the NIH in the form of a Minority Biomedical Research Support award for faculty development, student involvement in research, and enhancement of the research environment. This was followed by awards from the Macy Foundation and additional types of support from the NSF and NIH. In the meantime, the University created four Ph.D. programs--in chemistry, biochemistry, biology, and cellular and molecular biology. Today we dedicate this building, supported primarily through private sector contributions--and, most interestingly, private sector organizations from across the nation.

No mystery surrounds the question of why government and industry have come to see academic institutions as the logical focus for support of health and other kinds of research. In a 1945 policy report, Vannevar Bush, the President's Science Advisor, stated it succinctly: "Universities are the wellsprings of knowledge and understanding. As long as they are vigorous and healthy and their scientists are free to pursue truth wherever it may lead, there will be a flow of new scientific knowledge."<sup>2</sup> Just to state the size of the current budget of the NIH--about \$5.1 billion--is a way of summarizing the policy decisions affecting Federal support of biomedical research since World War II. The fact that four-fifths of that NIH budget is expended in grants and contracts awarded to outside organizations--mostly academic institutions--is in turn an eloquent statement of government reliance upon our partners in academia.

Industry's involvement with academia in research traditionally has been modest. Of all funds going to academic institutions for health R and D, for example, industry's share is about 3 percent as compared with 77 percent from the Federal Government. It is just recently, since about 1978, that industry has become a strong factor in the biomedical research coalition. Let me cite just a few statistics that indicate the scope of collaboration in health research and development among government, academia, and industry--and the different assignments we each perform within that collaboration. Remember that nearly 60 percent of all research funded by NIH is performed by universities.

Total national support for health R and D in 1983 was an estimated \$10.4 billion. Of that total, 36 percent was supported by NIH, 38 percent by industry, and 26 percent by other federal, state and local governments and private non-profit associations. But when we look at all basic health research support, which totaled some \$2.8 billion, 63 percent was provided by NIH and only about 10 percent by industry.

Breaking down those figures further, by type of effort supported, we find these comparisons: NIH support in 1983 was allocated approximately 61 percent to basic research; 31 percent to applied research, and 8 percent to development. Our internal analysis of statistics from various sources found

a different, but anticipated, trend in industry support: only 10 percent for basic research, 48 percent for application, and 45 percent for development.

It is clear, then, that government and industry perform complementary roles in the advancement and application of biomedical and other scientific knowledge.

Why this relatively new interest on the part of industry in the academic institution? One major force drawing industry toward academic institutions is the promise of biotechnology--a topic I want to spend a little time talking about because it will no doubt have an impact upon us all. Biotechnology might be defined as any technique that uses living organisms (or parts of organisms) to make or modify products to improve plants or animals, or to develop microorganisms for specific uses. It would include work involving DNA recombination and monoclonal antibodies, which I understand are among the projects planned for the new research building. For this new challenge, geneticists, immunologists, biophysicists, computer scientists and others have combined forces to extend the range of cell biology studies into areas previously unapproachable.

Biotechnology has much to offer in the biomedical arena, but goes well beyond into other scientific disciplines--a most remarkable aspect of biotechnology is its diverse impact. We can confidently expect to have available a new set of products that are of biological origin but are exquisitely specific in their effect. This may well change our whole approach to drug treatment and lead to drugs with fewer side effects but enhanced therapeutic impact. In other areas, industry will use biological reactions rather than the standard chemical processes to carry out tasks such as cleaning up oil spills and toxic wastes. This biological method should be much cheaper and more efficient, and should leave fewer unwanted by-products. In the agricultural area, new strains of plants and animals can be developed by methods that are much faster and more efficient than the classical breeding methods. Other applications are to be found in food processing and production, waste disposal, and in the production of a myriad of chemicals.

Industry, it seems, has awakened to the long-term commercial value of the research activities of academic institutions. As Barbara Culliton of Science magazine put it, "For the first time, in basic biomedical research, the university has something extremely valuable to sell."<sup>3</sup> That commodity is very, very precious. It is excellence and creativity. The men and women working in science in the universities and medical schools expanding the frontiers of science. Industry is beginning to realize that in the long-term they would benefit from a more intensive involvement with academia.

Credit must be given here, too, to academic institutions such as the Atlanta University Center for recognizing their potential value to industry and for actively seeking industrial support.

In several ways, the Federal Government is the "silent partner" in the new biotechnology partnership, yet, a very vital partner. What can be overlooked in all the excitement about the coming applications of biotechnology



is the solid foundation of basic research in the life sciences that undergirds these current efforts. Research done in the universities and medical schools around the country, most of it supported by the NIH, has moved from the use of simple model systems such as bacteria to more complex ones such as human cells, which could not be studied at the molecular level without recombinant DNA and hybridoma techniques. A recent article in the Washington Post about biotechnology stated, "Although universities, venture capitalists, scientists, and entrepreneurs all have played key roles in the industry's growth, the critical factor has been 30 years of growing support for basic biomedical research."<sup>4</sup> Scientists supported by NIH had no idea that their research would eventually contribute to the development of gene splicing, a crucial breakthrough that would lead to recombinant DNA technology. Arthur Kornberg, who won a Nobel Prize in 1959, put it in personal terms in a recent essay: "In these explorations (on basic aspects of DNA and RNA) I neither anticipated nor promised their industrial application. Nor did any of my colleagues with comparable federally funded projects." "In short," he said, "the genetic engineering industry spread out before us sprang entirely from the pursuit of irrelevant research in universities, made possible by the investment of many hundreds of millions of dollars by federal agencies over more than two decades."<sup>5</sup>

The contributions made by NIH in training biomedical scientists must be added in when assessing the science base that launched the biotechnology era.

Translating the commitment to biotechnology into dollars—in Fiscal Year 1984, NIH support for basic research and training related to biotechnology was estimated to total about \$497 million for directly related research and \$1.1 billion for the broader science effort. These two figures represent 11 percent and 25 percent of the total NIH research budget.

Industry deserves its credit too, because to further quote Dr. Kornberg, "science and technology are interdependent and often inextricably linked. The work done in universities over the years under federal support by scientists trained under federal support, could not have been possible without commercial contributions. When advanced instrumentation and fine biochemicals become commercially available and affordable, research is extended a thousandfold. The explosive development of cloning and DNA sequencing over the past few years would have been impossible without scintillation counters, centrifuges, commercial sources of enzymes, radioactive nucleotides, plastics, and other instrumentation and materials provided through commercial marketplace."<sup>6</sup>

The new era in biotechnology potentially has so much impact upon us as individuals, as scientists, and as academicians, in addition to such great impact upon our national economy, that it has raised a national debate on several issues: for example, concern has been voiced about the ethical aspects and regulation of human gene therapy. A recent study by a congressional organization has concluded that human gene therapy that does not result in the passing of new genetic material to future generations poses no exceptional ethical concerns beyond any experiment involving human subjects.<sup>7</sup> Nevertheless, many questions, now being considered by NIH, remain about guidelines that surround this kind of research.

Concern has also been raised about the potential environmental impact of plant experiments that would involve field testing of genetically modified organisms. In fact, a lawsuit has stopped several such proposed experiments, one of which is designed to prevent frost damage to plants. Policy discussions have begun about how to oversee biotechnology-based experiments so that we can all benefit from their results, while still protecting the environment from any danger that may exist.

To date, NIH has been the primary federal agency with guidelines covering work with recombinant molecules, but more recently, in order to accommodate the movement of the field beyond biomedical concerns, a new sort of "super recombinant DNA committee" has been proposed that would include such agencies as EPA, USDA, FDA, etc., as well as the NIH.

I mention these larger policy matters in this setting because academia has traditionally been a major contributor to national policy discussions of this sort. In fact, I note in the prospectus for the Science Research Institute that several science policy courses have been contemplated, among them one on recombinant DNA policy.

In addition, Dr. Luther Williams will be involved in national level discussions on biotechnology with the NIH Director's Advisory Committee. In June, that committee will meet to focus specifically on the future role of NIH in the biotechnology era.

It comes as no surprise that biotechnology is of national interest at this time--its future may play a large role in the prospects for the national economy. Right now, the U.S. is the world leader in most areas of biotechnology, with more companies, products, scientists and government support than anywhere else. The challenge now is to maintain and expand the country's competitive position. A recent government report determined three factors that are of overriding importance: government funding of basic and applied science, adequate numbers of trained personnel, and availability of funds for industrial development.<sup>8</sup> The report, of course, presupposes academically trained and academically based scientists and their key role in the future of biotechnology.

And this point brings us full circle from the Science Research Institute to the national policy scene and back again. In closing, I would like to quote once more from Dr. Kornberg's insightful essay. He said, "I am confident that within five years the most exciting prospects for medicine and industry will be subjects and products that no one now even talks about. Which scientists will be sensitive to these new opportunities and what organizations will be equipped to seize them?" I am confident that scientists affiliated with the Science Research Institute will be among those scientists and that this new building will contribute to their development.

0

## REFERENCES

1. Unpublished essay, "Biology and Technology,"  
Arthur Kornberg, 1982.
2. Vannevar Bush, "Science--the Endless Frontier," 1945,  
Report to the President on a Program for Postwar  
Scientific Research.
3. Culliton, B.J., "Biomedical Research Enters the Marketplace,"  
New England Journal of Medicine, 403:1195-1201, 1981.
4. The Washington Post, December 16, 1984.
5. Same as 1.
6. Same as 1.
7. "Human Gene Therapy: Background Paper," Office of Technology  
Assessment, U.S. Congress, December 1984.
8. "Commercial Biotechnology: An International Analysis,"  
Office of Technology Assessment, U.S. Congress, 1984.
9. Same as 1.



# INTRODUCTION OF SENATOR JACOB JAVITS\*

by

JAMES B. WYNGAARDEN, M.D.\*\*

We are greatly honored, Senator Javits, to have you as a guest at the National Institutes of Health. I am certain that Dr. Goldstein and his co-workers feel a special sense of pride from the fact that you have joined them for their 13th annual Institute-wide staff meeting.

The name "Jacob Javits" has been well known across the Nation and throughout the world for more than three decades. In your public career, Senator Javits, you were widely known for your leadership, for your vision, and for your humanitarian accomplishments. You have made significant contributions in many different areas of national concern. We at NIH are delighted that your colleagues in the Congress--the men and women best acquainted with your years of service--elected to express their respect and admiration of you through the establishment of awards in your name for research in the neurosciences.

The awards themselves bear the mark of your breadth of vision. Once the decision had been made to set up the awards in your honor, you wisely counseled that narrow earmarking be avoided--that specific mechanisms not be prescribed. This flexibility has permitted us to develop mechanisms for the support of research and for the preparation of clinical investigators that promise accelerated advancement of our understanding of neurological and communicative disorders.

Furthermore, we consider the Javits awards to be prototypes of valuable new mechanisms to be added to our current portfolio of measures for the funding of research throughout the NIH.

Senator, the NIH is grateful to you for your leadership and influence and I am happy to have this opportunity to say so.

It is now my pleasure to present -- Senator Jacob Javits.

---

\*NINCDS All Employees Meeting, ACRF Amphitheater, March 25, 1985, at 1 p.m.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



STATEMENT BY  
JAMES B. WYNGAARDEN, M.D.  
DIRECTOR  
NATIONAL INSTITUTES OF HEALTH  
PUBLIC HEALTH SERVICE  
DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE  
SUBCOMMITTEE ON HEALTH AND THE ENVIRONMENT  
OF THE  
COMMITTEE ON ENERGY AND COMMERCE  
U.S. HOUSE OF REPRESENTATIVES

MARCH 29, 1985



Mr. Chairman and Members of the Subcommittee:

I am pleased to appear before the Subcommittee on Health and the Environment to discuss the recent progress of biomedical research at the NIH. It is especially gratifying to report such advances in this setting, Mr. Chairman, because you and the members as well as the staff of the Subcommittee have shown such personal interest in the role of biomedical research in improving the health of the American people.

For about 40 years, the NIH has been the principal source of support for the health-related research conducted in America's universities and medical schools, currently supplying almost two-thirds of the funding for such research. The research supported by the NIH, together with that conducted in its own laboratories, has had a profound and beneficial influence on the modern practice of medicine and on the state of health of people throughout the Nation. The vision and persistence of the many who have championed the NIH over the years have been more than amply vindicated.

While the improvement of health is and will continue to be our central purpose, there has been substantial interest of late in a related development, one not foreseen when NIH was established--that is--the beginning of an entirely new industry based on the results of fundamental research for which the Agency was largely responsible. The influence of NIH on biotechnology has been substantial and extensive. A local example of this influence was reported in a recent article in the Washington Post that credited NIH research with helping to spawn more than 200 biotechnology companies in the Washington area alone. But the influence is international in scope. Recent

government and private industry studies attest to the NIH role in fostering this Nation's leadership in biotechnology. The NIH Director's Advisory Committee will devote the entire agenda of its June 1985 meeting to a discussion of that role.

In commenting on the essential relationship existing between the conduct of research by the NIH and the practice of medicine, I should take note of two events of the past year that are symbolic of an increasing awareness of such ties.

A special issue of the Journal of the American Medical Association, last October, devoted almost 50 pages to descriptions of the entire range of activities of the NIH to tell, in the words of the news editor, "what the existence of the NIH means for the practice of medicine."

In January 1985, another widely circulated publication, Medical World News, devoted much of its 25th anniversary issue to the National Institutes of Health. In the lead editorial, the comment was made that "few of the mainstays of clinical practice today have not had their origins in NIH research . . ."

Communication with both the health care and the biomedical research communities, making full use of advanced technology, continues to be an important function of the NIH's National Library of Medicine.

Briefly, I will mention a few of the highlights of research accomplishments by scientists working in or supported by the various components of the NIH:

- o There has been important progress on acquired immune deficiency syndrome (AIDS), particularly from the NIH laboratory of Dr. Robert Gallo. Dr. Gallo and French scientists independently discovered a virus that is the causative agent of the disease. More recently, the entire genetic structure of the virus has been mapped. This opens the way for new treatment opportunities and prevention strategies and will accelerate work aimed at vaccine development. Moreover, Dr. Gallo's method for detecting the AIDS virus antibody has led to the development of commercial test kits to screen blood and thus protect the Nation's blood supply.
- o NIH intramural scientists, also using genetic engineering techniques, have cloned the entire gene for the major antigen on one life cycle stage of the human malaria parasite Plasmodium falciparum. This discovery will allow preparation of sufficiently large quantities of the antigen to test for its potential use in a vaccine. Malaria is an important and growing world problem, due to increasing numbers of drug-resistant parasites and insecticide-resistant mosquitoes that are overwhelming ongoing control efforts.
- o A study supported by NIH at several centers has shown that clots in blood vessels of the heart can be dissolved by administration of an



agent rt-PA (tissue-type plasminogen activator) in patients developing heart attacks. This trial confirms that the agent can reopen blocked vessels quickly and probably without some of the side effects of other clot-dissolving agents. The treatment, with further study, may represent a major advance in the care of the 680,000 patients annually who experience a blood clot in the coronary vessels.

- o NIH intramural scientists have succeeded in developing a vaccine that promises to be effective against herpes simplex virus--the virus that causes "cold sores" or "fever blisters" on the skin or mucous membranes. The researchers used a technique developed at NIH--whereby herpes virus DNA is inserted into Vaccinia virus to produce a recombinant or hybrid virus. The genetic material of hepatitis B, of rabies, and of almost any organism can be inserted into Vaccinia virus. For rabies, influenza, and hepatitis B, very good protection can be induced in experimental animals.
- o In another clinical advance, NIH intramural scientists have found that the drug cyclosporine can rapidly reduce eye inflammation in patients with posterior uveitis, a serious disease that can severely limit vision. In most cases, vision also improved with control of inflammation.
- o The Division of Research Resources provides for the development, support, and administration of research resources and operates five distinct programs. The Clinical Research Program supports 76 General Clinical Research Centers (GCRCs). These specialized centers provide environments for investigations into the prevention,

diagnosis, and treatment of human disease. It is in these centers that laboratory findings can be evaluated for their ability to improve human health. The spectrum of research conducted in the GCRCs includes all the fields of clinical research supported by the NIH research Institutes such as immunology, cancer, nutrition, and diabetes. Examples of recent scientific accomplishments include: developing a treatment for a painful and disabling side effect of kidney dialysis; a new approach to surgery for inflammatory diseases of the large intestine (such as ulcerative colitis) which prevents post-surgical incontinence of feces; the prevention of calcium-containing kidney stones by administration of a drug that reduces crystallization of the salts that form the stones.

- o Scientists at NIH and others supported by NIH grants continue to discover more potential cancer-causing genes (oncogenes) and "map" their locations on human chromosomes. Such studies continue to confirm the role of these oncogenes in the origins of cancer. Further study may reveal ways to destroy or block the products of these oncogenes, and result in advances in cancer prevention, diagnosis and treatment.

Mr. Chairman, we are convinced that early exposure to research is an important factor in attracting bright and dedicated medical students into biomedical research. Much of today's most challenging research requires individuals who are both medically knowledgeable and scientifically trained.

The National Research Service Awards sustain this excellence in the training of future generations of biomedical scientists who will explore new ideas and add to our knowledge. Two special research training activities, supported by the NIGMS, are focused on areas of special need. The Medical Scientist Training Program (MSTP) is designed to increase the number of scientists who are both medical doctors and trained researchers and who can bring basic research into the clinical setting. The Minority Access to Research Careers (MARC) Program is designed to increase the numbers of minority scientists and has had a substantial effect on improving the science curricula at minority institutions.

Mr. Chairman, the directors of the constituent bureaus, institutes, and divisions of NIH have accompanied me to provide further information about accomplishments in their respective areas of responsibility.

I will confine my comments to matters that affect the NIH as a whole, addressing particularly the novel features of this year's proposal.

The funding for NIH research as established in the FY 1985 appropriation bill envisioned an economy that shortly after the signing of the bill turned out to have a less promising outlook than had been anticipated. The Nation is facing a very large budget deficit and the decision was made to restructure the Federal budget to minimize the need for spending increases between 1985 and 1986.



Therefore, the basis for development of the Fiscal Year 1986 budget for the NIH is the Administration's policy essentially to freeze domestic programs at the 1985 funding level. To accomplish this purpose without upsetting the stability of our major research support program requires adjustments in FY 1985 spending with regard primarily to the funding of research grants. In that light it was decided to freeze the number of new and completing projects at the "policy level" of 5,000 awards.

As the Secretary testified before the Senate Appropriations Committee, if we were to award 6,526 new grants for 1985, we would have to add \$307 million for continuation costs in 1986. This would have put downward pressure on the number of new and competing grants. An alternative freeze posture would have been to freeze the dollar amount allocated to research project grants at the 1985 level resulting in about 4,000 new and competing grants and to make offsetting reductions in other research mechanisms such as R&D contracts and research training awards. This was considered unacceptable.

The concept of using funds for the obligated purposes by forward funding through the two subsequent years will provide for the continuation of 5,000 new and competing grants and ensure a sense of stability and equity for NIH--not only this year, but in the future. In this regard, it was felt by the General Counsel at HHS and the General Counsel at OMB that this is within the statutory authority of the Department, and, therefore, no rescission would be needed.

Research project grants to individual investigators continue to receive the highest priority because they support the primary source from which fundamental discoveries emerge. Thus they represent the key mechanism in Federal support of biomedical research. The 1985 budget will fund 5,000 new and competing renewal research project grants and approximately 12,172 continuation awards arising from competition in previous years. About 646 of the 5,000 new and competing renewal awards will receive funding in 1985 for three years of support. This multiyear funding policy is intended to avoid significant fluctuations in the number of grants NIH is able to support and to lower future noncompeting requirements.

The 1985 budget also includes \$482,144,000 for 500 research centers. This represents an increase of four centers over 1984 and includes support for three new research centers on Alzheimer's disease and related disorders. As with research project grants, some of the research centers will receive multiyear support. Approximately 45 of the 500 centers will be awarded two years of support from FY 1985 funds.

Turning now to the 1986 budget, the request for NIH is \$4,852,680,000, a decrease of \$282,048,000 from the comparable 1985 level. Examined from a program level perspective, however, the request represents close to a 2 percent increase over 1985. This increase reflects the 1986 budget authority, plus the second year resources provided from 1985 funds. The budget request will support 12,957 full-time equivalent staff positions, a reduction of 150 from the 1985 level of 13,107, and a reduction of 704

from the 1984 actual usage of 13,661. The budget also assumes savings of \$29.8 million in administrative costs and \$19.1 million as the result of the proposed 5 percent reduction in pay costs.

The request supports an estimated 5,000 new and competing renewal research project grants and 11,242 noncompeting (i.e., previously competed) research project grants. Including the estimated 646 grants which were multiyear funded in 1985, the total number of active research project grants in 1986 will be 16,888. Direct costs of research project grants in 1986 will be funded on the average at the historical levels of 97 percent of costs recommended by study sections for new and competing renewal awards, and 99 percent of committed amounts for noncompeting awards. The NIH aggregate average costs will be approximately 6.0 percent higher than 1985 for new and competing renewal awards, and about 7.8 percent higher for noncompeting continuations.

The 1986 request includes \$412,391,000 to fund 455 research centers. The 45 centers that were multiyear funded in 1985 will remain active in 1986, thus a total of 500 centers will be ongoing in 1986, the same number as will be supported in 1985. The budget assumes the same average costs in 1986 as in 1985.

As part of the Administration's effort to hold domestic programs at the 1985 level, indirect costs rates associated with research grants will be held at the 1985 rate. It is estimated that this measure will save about \$23 million.



NIH will support approximately 9,900 research trainees in 1986; the same number is estimated to be supported in 1985. This represents about 94 percent of the level recommended by the National Academy of Sciences for the NIH. Consistent with the overall freeze guidance, stipend levels are maintained at their 1985 level which represents an increase over 1984.

Budget authority of \$561,653,000 is requested for intramural research in 1986. The decrease of \$17,638,000 from the 1985 level represents the savings resulting from government-wide reduction in administrative costs and the proposed 5 percent paycut.

In summary, the 1986 request for the NIH represents a realistic level of Federal support for biomedical research and research training in the context of the rising Federal deficit and the need for Federal fiscal austerity. The 1986 request reflects the Administration's commitment even in times of scarce resources to a stable program of biomedical research and research training.

I will be pleased to answer any questions you may have.



## "INSTITUTIONAL IMPACTS OF NIH INITIATIVES AND REFORMS"\*

by

James B. Wyngaarden, M.D.\*\*

This session of the 1985 AAAS R&D Colloquium addresses a subject that sooner or later constitutes a major, if not a decisive, element in most policy decisions of the National Institutes of Health. We must take into account the effect of our actions on the more than 1,200 institutions that receive NIH support for biomedical research. But our concerns about the impact of our initiatives on the grantee community extend beyond those that are generated in the usual arms length agency/client, grantor/grantee relationships. For we are all a part of the biomedical research community with complementary resources and mutual obligations.

### The NIH Partnership With Academia

Four-fifths of the NIH budget is devoted to funding extramural research and research training. About three-fourths of those extramural expenditures are made in support of research and research training at universities and schools of the health professions. On the other side of the coin, over 60 percent of health related R&D conducted in institutions of higher education is supported by the NIH.

Because the vigor and productivity of NIH programs are in large measure attributable to our partnership with academia, difficulties that confront research programs in universities and health professional schools confront us as well. Many of our initiatives and reforms are intended to help institutions deal with changing circumstances as, for example, budget uncertainties that arise from a multiplicity of causes, including Federal actions. We are especially concerned that NIH programs serve not only their mandated purposes but that they contribute actively to the nurture of the scientific enterprise, and the stability of institutions and scientists.

With these purposes in mind, we have given increasingly higher priority to the support of investigator-initiated research. We consider such grants the most effective means for stimulating and supporting the creativity of the biomedical research community.

Between 1972 and 1984 the annual NIH appropriation in current dollars was essentially tripled, increasing from \$1.5 billion to \$4.49 billion, but the amount awarded for research project grants

---

\*Address, Tenth Annual AAAS Colloquium on R&D Policy, Capital Hilton Hotel, Washington, DC, April 4, 1985.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



more than quadrupled. Specifically, the totals awarded for the traditional project grants (R01) and program project grants (P01) grew from \$551 million in 1972 to \$2.4 billion in 1984. The total number of such project grants being supported during 1972 was 10,290 and last year we supported 17,305.

The numbers I have recited are but reference points to which can be related major shifts made by the NIH over the past 10 to 15 years. These changes were made in a determined effort to protect the productivity and stability of our grant-supported programs and to ameliorate the effects of tightened Federal budgets on our extra-mural partners.

There was no abrupt, one-shot reform initiative but a series of incremental adjustments, whose cumulative effect over a decade has threatened the balance of the array of essential mechanisms employed by the NIH in carrying out its programs.

In the interest of protecting the individual investigator and preserving the principle of the scientists' initiative in research, the NIH stretched itself to the limit of what could be done.

The leveling off of the NIH year-to-year budget increases in the face of the fiscal constraints of the 1970s was not the only pressure. Indirect costs took an increasing share of the grant dollar, rising from 21 percent in 1972 to over 31 percent in 1984. However, a greater pressure developed from the rapid growth of science. The number of excellent applications for grants increased at a much more rapid rate than our ability to fund them.

The number of competing applications for research projects reviewed in 1984, 16,900, essentially doubled the count of those reviewed in 1972.

In summary, during the period from 1972-1984, when the NIH budget grew by about 28 percent in real dollars, we have increased the number and budget of project grants by about 70 percent. This increase was made possible by shifting the share of the total NIH budget dedicated to project grants from 37 percent in 1972 to more than 53 percent in 1984. A consequence of this shift is a reduction in the share for research contracts from about 15 percent to 7.7 and the share for research training from more than 10 percent to 3.7.

At one point in this period when, after 1979, our constant dollar budget began to decline and all possible shifts among program mechanisms had been made, a kind of last ditch approach was taken to maintain the number of active project grants by negotiating downward the costs of new and competing renewal grant proposals as well as the noncompeting project grants.

In fact, the President's budget proposal for 1984 was premised on reductions in competing proposals of 10 percent from the levels recommended by study sections. A 5 percent downward negotiation

was projected in the budget submitted for 1985. Congress restored most of these funds, making systematic downward negotiations unnecessary.

I am pleased to report that the President's budget request for 1986 proposes no such reduction and allows inflationary increases for research projects. The direct costs of research project grants are estimated at the historical levels of 97 percent of study section recommended costs for new and competing renewals and 99 percent of committed amounts for noncompeting awards.

Arbitrary downward negotiation of grants was viewed by NIH as a seriously damaging approach to the solution of financial stringencies and we strongly resisted continuation of the practice.

Inasmuch as the award of investigator-initiated research project grants is considered our prime instrument, we have regarded maintenance of the viability of that mechanism as a highest priority.

The number of competing awards has fluctuated greatly over the 13-year period, ranging from a low of 2,592 in FY 73 to a high of 5,944 in FY 1979. It is our perception that such fluctuations not only create financial problems for academic institutions but adversely influence the career decisions of medical and graduate students, as well as young physicians and scientists.

We recognized that to assure future health gains, the current national research capability must be sustained and enhanced. As applied to research project grants, a major goal was to minimize the year-to-year fluctuations in the numbers of new and competing renewal awards. The goal of funding at least 5,000 new and competing renewal grants, atop a base of moral commitments of 11,000 noncompeting continuation grants, was considered a major feature of the "stabilization" policy.

While we have supported at least 5,000 new and competing renewal research project grants each year since 1980, it would be incorrect to contend that the maintenance of this number per se has produced stability for the biomedical research enterprise overall.

#### Increased Competition and Some of its Effects

Earlier I mentioned the increasing numbers of research proposals, and particularly the numbers of excellent applications. These increases have outdistanced the funds available. In 1972, we were able to fund about 59 percent of grants eligible for award, but in 1984 the award rate was about 37 percent.

From the NIH perspective, the approved but unfunded grants constitute an index of the scientific opportunities that we currently are unable to pursue. From the viewpoint of the applicant, these figures mean that an increasing number of investigators, whose research careers often depend upon successful competition for grant support, are failing to obtain that support.

Another measure, perhaps more meaningful to the applicant, is the success rate that is the ratio of the number of awards to the number of applications reviewed. In 1972 the success rate was 42 percent--in 1984 it was 32 percent, a 24 percent decrease in success rate compared with a 37 percent decrease in award rate.

The priority scores being assigned by reviewers reflect the escalation of excellence, and scores increasingly are compressed, shifting the pay lines.

Increasingly, grant proposals are being resubmitted after unsuccessful competitive review. In 1979, 14 percent of applications reviewed were resubmissions--in 1984, 23.9 percent, almost double the portion of proposals under review, were resubmissions.

This situation is both a result and a cause of increased competition.

#### FY 1985 and FY 1986 Budgets

The budget for NIH for Fiscal Year 1985, passed by the Congress late last year, was \$5.15 billion. This budget went into effect with the start of the new fiscal year on October 1, and provided resources for 6,529 new and competing research project awards. The election on November 4 was widely interpreted as carrying a message to the new Administration to address the deficit by reducing government spending and without increasing taxes. The final touches were put on the FY 1986 budget proposal in late December. At that time, OMB also decided to reduce our allotment of new and continuing awards to 5,000 for 1985, and instructed us to use the saving resulting from not funding the additional 1,500 grants for multiyear funding of about 650 awards. Thus, only 4,350 of the 5,000 awards made in 1985 will be represented in the commitment base for Fiscal Years 1986 and 1987. A similar ploy was ordered for 33 of the 500 new and competing centers authorized for 1985. These two measures together were calculated to provide a savings of almost \$1 billion in the ensuing fiscal years. This budgetary rearrangement was designed to provide a stable number of 5,000 new and competing awards in both fiscal years, in spite of a reduction in the total NIH budget of \$287 million in 1986. A combination of the original Congressional budget for 1985 and the President's request for the NIH for 1986 would otherwise have supported 6,529 new research project starts one year and only 2,100 the next. The proposed revision of the 1985 budget has occasioned a vigorous negative reaction from the extramural community. Also just recently, the Comptroller General has ruled that multiyear funding in the absence of specific Congressional intent is illegal. The Department of Health and Human Services and the OMB are studying the Comptroller General's opinion and are planning to respond to it. In my view, it is highly desirable that this issue be settled quickly, for at present we are holding back substantial amounts of funds in order that we can make multiyear awards if that is the ultimate instruction. Of course, we do not know what Congressional action on the 1986 budget will be. For the past 15



years at least, Administrations have tended to request modest increases for NIH, since Congress has tended to add to the requested budget. In fact, the figures from 1970 through 1984 show that Administration requests averaged 2.7 percent over the previous year, and Congressional action 8.4 percent. At present, Congress is awaiting a budget resolution and will probably coordinate its response to the proposed revision of the 1985 budget with its recommendations for 1986.

#### Possible Adjustments to Improve Efficiency of the Granting Process

These things are happening at a time when the universities are least able to provide institutional sources of flexible funding to offset the uncertainties inherent in research projects. While it is not possible for the NIH to reverse the major trends of fiscal constraints, we are examining carefully the question of whether certain attributes of the current extramural awards system may be making the grants application process more burdensome than necessary for the investigator, the university, and the NIH peer review system.

We are also looking into the question whether our current mechanisms or systems contribute to uncertainty and instability in the careers of scientists and create impediments to their productivity.

It has been suggested, for example, that one of the factors that may be contributing needlessly to the workload of both the grant applicant and the NIH peer review system is the excessive complexity and sheer bulk of the research grant application. Inasmuch as the NIH peer review system is itself made possible only by sacrificial contributions of the time of non-Federal scientists, we must be sensitive to any unnecessary compounding of their task, as well as the task of the applicant.

Some think that the large size of applications may be the result of a tendency on the part of study sections, confronted with a large number of excellent applications, to attempt to establish what is wrong with a research proposal rather than what is right about it. Such behavior may create the impression among applicants that comprehensive detailed documentation of all aspects of a proposal is required to assure success. The submission of a detailed proposal, in turn, may encourage the study sections to concentrate on narrow technical details rather than the overall merit of the grant application.

It was observed in a recent study that only about 40 percent of the principal investigators who received their first NIH project support were able to compete successfully for continued NIH research grant support. We are considering the possibility of extending the period of award for first-time research project grants as a means for diminishing the inefficiency and waste of

intellectual resources created by the need for investigators to expend relatively large amounts of time and effort in applying at frequent intervals for support. We are aware of the possible inequity created by requiring a new investigator to justify continued research support when that individual has only a limited time in which to produce evidence of research accomplishments. Overall, the average "longevity" of a principal investigator on an NIH research grant is approximately seven years.

In recognizing the unique strengths of established investigators, ways are being considered to provide longer, more stable research grant support for these outstanding scientists and to modify the criteria and methods by which they are selected for continued support.

But the suggested reforms entail more than administrative adjustments. Their budgetary consequences would be substantial and in the absence of major funding increases could reduce the number of new and competing renewal grants.

#### Defining the Current Mission of NIH

At the beginning of the talk, I stated that "we are especially concerned that NIH programs serve not only their mandated purposes but that they contribute actively to the nurture of the scientific enterprise."

There is no simple statement of the "mandated purposes" of the NIH in the several statutes authorizing its programs, but the purpose is clear. One unofficial statement in use for several years describes the purpose of NIH in the following language: "Its mission is to uncover new knowledge that will lead to better health for everyone." Recent developments, however, could call the adequacy of that mission statement into question.

Increasingly, NIH-conducted and NIH-supported research is being credited with initiating as well as helping to sustain the spectacular growth of biotechnology. Many of the anticipated products of the new technology bear little direct relationship to health, and our studies in molecular biology are being viewed primarily by some as necessary steps toward maintaining our national supremacy in an international race for the development of new technologies.

#### Basic Research and Technical Superiority

The potential yields from our new insights into molecular biology are only beginning to be realized. There is a new awareness in the higher councils of government that basic research represents a new national frontier that promises rich economic rewards. The suggestion has been made that the Nation's interests would better be served by bringing all federal research agencies together in one new department of science. On the surface the plan seems attractive. Science agencies have unusual organizational and

administrative needs, particularly having to do with such matters as pay scales for highly trained scientific personnel. Notwithstanding certain possible advantages, the NIH does not favor the idea of being included in a department of science because our primary concerns are related to health.

It is true that we relate to the greater scientific community and support substantial amounts of research in the Nation's graduate schools, but almost 60 percent of all the funds we award in our extramural programs go to health professional schools and hospitals. Further, the NIH is a strategically important and necessary complement to the other agencies of the U. S. Public Health Service.

There is currently no move that we are aware of to follow up on earlier discussions of a department of science, but the role of NIH in stimulating progress in biotechnology has received significant public attention. In late June, the Director's Advisory Committee will examine the issues and implications of this de facto expansion of the NIH mission.

Industry is increasing its investment in research and development. In 1983, the total of annual industrial expenditures for health-related research and development in this country for the first time in recent history exceeded the amounts expended by the NIH for similar purposes.

Even though industry as a whole is now spending more than the NIH, the bulk of such outlays is for developmental studies and responsibility for basic research continues to rest heavily upon the Federal Government.

#### New Partnerships: Academia and Industry

Within the past few years, industry has entered direct relationships with a number of outstanding health professional schools and research hospitals for the support of medical research. The mechanisms established for such collaboration vary from institution to institution, but the ones I know about appear to have taken carefully into account the need for freedom of inquiry, so essential to scientific productivity.

The NIH role with regard to these new partnerships has been that of a facilitator when needed, but we have not felt that we should take an active part in establishing such relationships nor that we should presume to prescribe formats or mechanisms for accommodating this third partner. I have said previously, however, that notwithstanding the fact that the areas of collaboration between the universities and industry have broadened considerably and promise to continue in that expansion, I believe it entirely predictable that the Government will continue as the principal source for funding for basic research.



For the past twenty minutes or so I have suggested a number of issues of concern to both the NIH and our partner institutions in the research enterprise. I would be glad to discuss further the points I have raised or to engage with questions from the audience.

LLOYD H. SMITH, JR., M.D.

I first met Holly Smith as a fellow intern in Medicine at the Massachusetts General Hospital in July 1948. Holly had spent an extra student year with George Thorn and John Merrill, and as a consequence we were contemporaries. That was my good fortune, for out of the camaraderie of house staff experiences grew a lifetime of friendship and collaboration.

After residency training, both of our interests gravitated toward metabolic diseases and biochemical mechanisms. During his tenure as a Harvard Junior Fellow, Holly spent a year in Sweden working in pyrimidine metabolism with Reichart, "To find out what journals the King read so I would know where to publish." We both spent a year with DeWitt Stetten Jr., in New York, although at different times. For many years our chief contacts were at the Atlantic City meetings, where Holly's laboratory was usually represented on the plenary session, and where with Johnny Knowles and others we usually spent one evening at the Jockey Club. One year Holly persuaded Walter Bauer to come with us. Bauer seemed to have had a great time, but later remarked that he could not believe a nice fellow like Holly would take him to a place like that!

The first time Holly and I found ourselves on the same program, he talked on pyrimidine metabolism and orotic aciduria, and I on purine metabolism and gout. Holly's talk was witty, engaging, authoritative and well illustrated, and drew rave

reviews. I resolved to collect better stories and prepare more artistic slides.

On two occasions we found ourselves working on the same research problem, though not by design: a purine 3' phosphoribosyltransferase activity discovered and purified in my laboratory turned out to be orotic acid phosphoribosyltransferase, an enzyme Holly's group had found deficient in orotic aciduria; and our studies on synthesis and turnover of oxalic acid were conducted in parallel with Holly and Hibbard Williams' first study on hereditary oxaluria.

In 1963-64 both of us took a sabbatical leave. Holly went to Oxford from the MGH, and I to Paris from Duke. At Christmas, the Smiths showed us Oxford University, the Deer Park and the grounds of Blenheim Castle. In the Spring we sat in a bistro in Paris as Holly in high excitement told us of his decision to accept the Chair of Medicine at the University of California in San Francisco.

Several years later I had the privilege of serving as a Visiting Professor in Holly's Department. He showed me the view of San Francisco from atop Moffitt Hospital, where he was accustomed to putting the final recruiting arm around an aspiring faculty candidate. Strangely, the event reminded me of the story of Christ on a high mountain when He was offered all the kingdoms of the world if He would yield to temptation. On the weekend we motored down the coast, enjoyed wine and cheese on the beach, and visited the campus at Santa Barbara. Later, Holly and Marg returned the favor at Duke.



Holly and I served together for a time on the President's Science Advisory Committee, until Mr. Nixon abolished the panel in pique over the testimony of one of our members against the SST. We overlapped for about six years as councillors and officers of the Association of American Physicians. As members of the Medical Advisory Board of the Howard Hughes Medical Institute for ten years, we met several times each year in Miami or at a school with an HHMI unit -- good science, bright young investigators, splendid colleagues adroitly led by George Thorn, marvelous food and wine, and (at least in Miami) always tennis, resuming friendly competition after a 25 year hiatus.

But the activity that has been most enriching for me has been the shared editorship of the Cecil Textbook of Medicine since 1978. This activity has required numerous meetings and continuous communication. Holly is a superb colleague. His human interactions are as full of intelligence, humor, and warmth as are his eloquent and entertaining speeches and his erudite and witty writings. As an enduring friend, Holly is in a special class. I'm glad this versatile and charismatic man doesn't work for Harrison!

James B. Wyngaarden, M.D.  
March 20, 1985



## WELCOMING REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

It's a pleasure to welcome you to the National Institutes of Health and this workshop on "Mapping, Cloning, Manipulating Genes: New Strategies for Understanding and Treatment of Inherited Human Diseases." I'm aware that many of you have come a great distance and I thank you for your interest and willingness to participate in these two days of discussions.

Until recently, research in metabolism has focused on the isolation and characterization of enzymes and metabolites, or the elucidation of the mechanisms of regulation of metabolic processes, mainly by means of classical biochemical or biophysical approaches.

Today, the recently developed techniques of molecular biology offer innovative approaches to the study of these enzymes and processes and related diseases.

Some of these new directions, to be amply discussed at this workshop, include mapping genes on human chromosomes, cloning human genes, detecting gene sequences by immunological methods, identifying mutations in genes and in their translated proteins and enzymes, targeting and inserting genes, transfecting cells, and lastly

---

\*NIADDK Workshop on Mapping, Cloning, Manipulating Genes: New Strategies for Understanding and Treatment of Inherited Human Diseases, April 18, 1985.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



transferring genes into somatic cells with the goal of correcting a primary defect.

Recent advances in cDNA sequencing methodology could help in elucidating the primary structure of enzymes which have been persistently difficult to isolate and characterize. Efforts in this area will most likely forward our understanding of metabolic regulation. The introduction of modified genes for metabolically important enzymes into host cells could result in new cell lines in which the regulation of a specific pathway can be studied.

Some laboratories are pioneering the use of retroviral vectors for introduction of genes into somatic cells. Even though, in some cases, the host cell incorporates the transferred gene with high efficiency, extensive research remains to be done on gene delivery into cells and insertion into chromosomes, the nature of tissue specific expression of various genes, the possible consequences of the inclusion of retroviral vectors in somatic cells, and many other topics.

The inborn errors of metabolism include hundreds of rare or very rare diseases. As a group, they cause extensive mortality, morbidity, and suffering. The etiology of many of these diseases is still unknown. Therapy for even more is still unavailable. I understand that you will consider these issues at this workshop. This is an area fully worthy of your efforts.

Here at NIH, in our intramural program, there is a longstanding tradition of excellence both in the study of inherited metabolic diseases and in the application of new genetic techniques to their understanding and treatment. I am delighted to see both

the intramural and extramural scientific communities interested in this area join together in discussing recent achievements and future directions.

The NIH is providing significant support to the extramural human genetics community, primarily through the investigator-initiated research project grant mechanism. This mechanism of support, which represents the core of the NIH extramural programs, provides individual investigators with the flexibility to pursue promising scientific opportunities wherever they might lead.

In closing, let me simply reiterate that it is our pleasure to host this meeting here today, and I hope that many future achievements in understanding and treating inherited metabolic diseases will originate here.





# NIH - AFTER ALMOST A CENTURY OF SCIENCE FOR HEALTH\*

by

JAMES B. WYNGAARDEN, M.D.\*\*

Around Bethesda these days, there is an increasing amount of talk about celebrating the centennial of the establishment in 1887 of the National Institutes of Health. There is new interest in the Agency's history as we plan to celebrate "A Century of Science for Health." Within the coming months, we will be announcing a variety of events and activities to mark the centennial. Today, however, I will take this opportunity to remind all NIH alumni--former staffers who have worked or been trained on the Bethesda campus--to visit the NIH booth in the exhibit hall and leave your current address. We will use the alumni mailing list to keep you informed about the reunion being scheduled for the fall of 1987, and to let you know of other observances being planned to celebrate the history of that truly unique institution. Today, I will be discussing some of that history but only in a limited sense. The first part of my presentation will be devoted to a brief review of the highlights of the NIH budget from 1945 to the present.

The 40-year period since the end of World War II is the era of the modern NIH--the Agency as we know it today. The war years brought dramatic changes to the small Federal laboratory known as the National Institute of Health. Almost all of its research activities until that time had been in-house, but under the stress of war, universities, medical schools, hospitals and other laboratories were drafted into a partnership with the Federal Government to meet the pressing needs for medical research. The partnerships that were formed in that period have never been dissolved. The NIH, that prior to 1940 had been almost exclusively an intramural operation, began by the late 1940's to rely more and more heavily upon its extramural programs in carrying out its mandate. In recent years, the commitment of funds to the extramural components has represented four-fifths of the Agency's total budget.

## History of the Budget

Addition of the extramural dimension to the NIH was accompanied by increases in budget--increases that for a part of the time from 1945 to the present has been spectacular. (Slides 1a, 1b, 1c, 1d, 1e)

Two major phases of our growth in the past 40 years are apparent from this set of slides. In terms of purchasing power in constant dollars, the total budget of NIH grew from 1945 to 1968 at an astounding average rate of 24 percent per year. The growth per year since

---

\*Address to the American Society of Biological Chemists at FASEB Meetings, Anaheim, California, April 24, 1985.

\*\*Director, National Institutes of Health.

1968, taking inflation into account, has been much less--about 2 percent per year.

In part, the extremely rapid growth in the earlier period resulted from expansion of the scope of the Agency through the creation one by one of new institutes. Increases since 1968 have tended to be selective with some components, programs and mechanisms enjoying substantial increases and other elements suffering compensating decreases.

Such adjustments have been at the heart of most budget-related policy discussions concerning the NIH for the past 15 years.

By the mid-1960's, it had become apparent that the steep climb in the NIH budget must taper off. To blunt this trend, however, dedicated proponents of our programs of biomedical research took the offensive under the banner of a war against the killers--heart disease, cancer, and stroke. The initial legislative outcome of the mid-60's initiative--the regional medical programs--was more a mechanism for the transfer of the results of research than an increase in outlays for research itself. But by 1970 a well-planned and expertly executed initiative was responsible for what was called a declaration of war against cancer. For a time, the Democratic Congress and the Republican Administration attempted to outbid each other in terms of appropriation and organizational innovations to hasten the conquest of cancer. Proponents of research on heart disease followed suit and were able to attract attention and funds.

Between 1971 and 1973, the budget of the National Cancer Institute in current dollars was more than doubled. It had tripled by 1975. The National Heart, Lung, and Blood Institute also experienced a period of rapid growth, increasing by 35 percent between 1971 and 1973 and doubling by 1977. The budgets of both these institutes grew faster than the total NIH budget during the early seventies and consequently most other components had reductions. By the late seventies, however, the growth differentials between institutes had largely evened out and a steady state had been reached.

#### Growth of the Research Project Grant Budget

An examination of the NIH budget for the period beginning in 1972 and continuing to the present would reveal another set of adjustments not along institute lines but shifts in the use of the various mechanisms we fund for carrying out research. The salient feature of these adjustments was the marked shift in the allocation of funds to favor the support of research project grants. In the period from 1972 to 1984, the budget for research project grants increased from 44 to 66 percent of the extramural budget, and that for all research grants from 62 to 84 percent. There was a concomitant reduction in budget for contracts and training. The total number of such project grants being supported during 1972 was 10,290, and by 1984 the number had grown to 17,305. Throughout this time, the average award per project remained virtually unchanged in constant dollars. However, indirect

costs took an increasing share of the research award, rising from 21 percent in 1972 to over 31 percent in 1984. Consequently, the real dollars available per project for direct costs were reduced. (Slides 2, 3, 4, 5, 6)

After 1979 when our constant dollar budget began to decline and all possible shifts among program mechanisms had been made, it was decided that in order to maintain the number of active project grants, our only recourse was to negotiate downward not only the projected costs of competing grants but also the continuing commitments for noncompeting projects.

The President's budget proposal for 1984 required reductions in awards for competing projects of 10 percent from the levels recommended by study sections. A 5 percent downward negotiation was projected in the budget submitted for 1985. Congress restored most of these funds making systematic downward negotiations unnecessary in the current year. In my view, arbitrary downward negotiation of grants is a seriously damaging approach to the solution of financial stringencies and I have personally strongly resisted continuation of that practice.

#### Growth of the Applicant Pool and the Stabilization Initiative

Another pressure has developed, not directly the result of the budget crunch, but an effect of the progress of science. The number of excellent applications for grants increased at a much more rapid rate than our ability to fund them. The number of competing applications for project grants reviewed in 1984 was 16,900, essentially double the number reviewed in 1972. (Slide 7)

In the past decade, we have become increasingly concerned about maintaining a relatively stable and predictable level of new and competing renewal project grants. The number of competing awards has fluctuated greatly since 1972, ranging from a total of 2,592 in FY 73 to a high of 5,944 in 1979. Such fluctuations not only create financial problems for grantee institutions but adversely influence the career decisions of graduate students as well as young scientists. (Slide 7a)

We have recognized that to assure future health gains, the current national research capability must be sustained and enhanced. As applied to research project grants, a major goal was to minimize the year-to-year fluctuations in the number of competing grants. The goal of funding at least 5,000 new and competing renewal grants atop a base of moral commitments of 11,000 continuation grants was considered a major feature of the "stabilization" policy. While we have indeed supported at least 5,000 competing research project grants each year since 1980, it would be incorrect to contend that the maintenance of this number per se has produced stability for the research programs of the NIH.



## Increased Competition and Some of Its Effects

The marked increase in the number of meritorious applications for grants characteristic of the past decade has outstripped the availability of resources and intensified competition.

In 1975 we were able to fund about 65 percent of grants eligible for award, but in 1984 the award rate was about 37 percent. (Slide 8)

From the NIH perspective, the approved but unfunded grants constitute an index of the scientific opportunities that we currently are unable to pursue. From the viewpoint of the applicant, these figures mean that an increasing number of investigators whose research careers often depend upon successful competition for grant support are failing to obtain that support.

Another measure perhaps more meaningful to the applicant is the success rate that is the ratio of the number of awards to the number of applications reviewed. In 1975 the success rate was 50 percent. In 1984 it was 32 percent.

The priority scores being assigned by reviewers reflect the escalation of excellence, and scores increasingly are compressed, shifting the paylines. Increasingly, grant proposals are being resubmitted after unsuccessful competitive review. (Slide 9) In 1965, 5.9 percent of applications reviewed were resubmissions--in 1975, it was 14.9 percent, and by 1985, we estimate the proportion of resubmissions to be 24.6 percent. (Slide 10)

Resubmitted applications in essence are proposals amended to remedy deficiencies identified in the review process, for the unsuccessful investigators endeavor to meet the criticisms spelled out in the Pink Sheet. As might be expected, resubmitted applications enjoy a higher success rate than de novo proposals. One undesirable result of the growing resubmission rate is heightened influence of the study section on the form if not the substance of grant applications. At the extreme, the study section's role can approach that of a committee designing a procurement instrument rather than evaluating objectively the merit of independently initiated research problems and the proposed strategies of investigation. When the peer review system operates in such a way as to alter the projects under review, the process takes on a similarity to procurement that inhibits the creative reach of the prime support mechanism we employ--the investigator-initiated project grant.

This subtle intrusion of the review process into the creative process is not wholly the result of resubmitted applications. Most applicants for grants are well acquainted with the operations of initial review groups. The great majority of applicants are aware that the competition is tougher than ever, both from sheer numbers of applications and from the quality of such proposals. The word gets around that in making difficult decisions among applications of essentially equal merit, study sections tend to make negative judgments--that is, to search for what is wrong rather than what is right about an application under review. Based on such folk wisdom, the

applicant tends to overdocument, to go to extremes to shore up whatever he or she perceives to be possible weak spots. As a result, the workload of the study section is increased and the possibly excessive detail supplied by the proposer becomes itself fair game for the reviewer seeking concrete grounds for distinguishing the best from a pool of excellent applications.

### The Awards Process Revisited

While it is not possible for NIH to reverse the trends of fiscal constraints that have been responsible for many of the difficulties I have been discussing, we are examining carefully the question of whether certain attributes of the current extramural award system may be making the grants application process more burdensome than necessary for the investigator, the university, and the NIH peer review system.

We are also looking into the question whether our current mechanisms or systems contribute to uncertainty and instability in the careers of scientists and create impediments to their productivity. It has been suggested, for example, that one of the factors that may be contributing needlessly to the workload of both the grant applicant and the NIH peer review system is the excessive complexity and sheer bulk of the research grant application. Inasmuch as the NIH peer review system is itself made possible only by generous contributions of the time of non-Federal scientists, we must be sensitive to any unnecessary compounding of their task as well as the task of the applicant.

It was observed in a recent study that only about 40 percent of the principal investigators who received their first NIH project support were able to compete successfully for continued NIH research grant support. We are considering the possibility of extending the period of award for first-time research project grants as a means for diminishing the inefficiency and waste of intellectual resources created by the need for investigators to expend relatively large amounts of time and effort in applying at frequent intervals for support. We are aware of the possible inequity created by requiring a new investigator to justify continued research support when that individual has only a limited time in which to produce evidence of research accomplishments.

In recognizing the unique strengths of established investigators, ways are being considered to provide longer, more stable research grant support for these outstanding scientists and to modify the criteria and methods by which they are selected for continued support. We believe that longer mid-career grants to established investigators would represent an efficient and prudent investment of Federal funds.

But the suggested reforms entail more than administrative adjustments. Their budgetary consequences would be substantial and in the absence of major funding increases could reduce the number of new and competing renewal grants we would be able to make in future years.

## Research Training

Permit me to turn briefly to another subject--an essential component of NIH activities--research training. There are two general categories of NIH training programs--namely, those funded through the National Research Service Awards (NRSA) and those encompassed in the more advanced career development series. NRSA institutional awards permit institutional selection of trainees at both the predoctoral and postdoctoral level. The Medical Science Training Program, supported through institutions within the NRSA program, is considered one of the most successful in building up clinical research, an area we believe to be critically important to the future. In this connection, I should mention that we shortly will announce the names of 25 medical students, who have been accepted under the joint NIH-Hughes Medical Institute Scholars Program, to spend 9-12 months in training at Bethesda.

Individual fellowships are also awarded through national competition under the NRSA. The level of stipends we have been able to pay has been of concern to potential trainees and fellows. I am pleased to report that the 1985 appropriation contained a substantial increase of funds earmarked for increased stipends. These increases were aimed primarily at making the clinical postdoctoral fellow and trainee income more compatible with that of the house staff salaries. Equity is maintained for the postdoctoral Ph.D. who, after two years of postdoctoral training, is contributing in an important way to research activity. Postdoctoral stipends have been increased so that with funds for tuition and other expenses, our total outlay per student per year is essentially the same as that offered by the National Science Foundation.

The options available through the NIH for advanced research preparation are offered through the Research Career Development or K series. The oldest of these is the Research Career Development Award solely for salary and fringe benefits. More than 80 percent of those who have received our RCDAs now have support for a research project grant. Other K series awards include the academic investigator award, the clinical investigator award, the mid-career development award, and the physician/scientist award. These awards provide a salary of up to \$40,000 plus applicable fringe benefits. The actual salary is to be comparable to that of others at the same institution at the same level of training and experience.

To summarize--a budget of over \$166 million in 1984 supported 10,514 NRSA trainees and fellows. Roughly one-third of such NRSA positions were allocated to predoctoral students, about half to postdoctoral trainees and fellows, and the remainder to special programs. In the career development programs in 1984, a total of over \$53 million supported 1,208 awards. It is our intention to maintain about a 50/50 ratio between M.D.s and Ph.Ds within the career development programs.



## The Infrastructure

The well-being of our research training programs is essential to the continuation of research progress. Such programs are more important in the 1980's than they were in previous decades because of the level of sophistication required of today's successful investigator.

The advances in science of recent years have also brought with them need for advances in instrumentation and facilities. Over the past decade, increasing concerns over the deteriorating institutional base for health research have been widely expressed. The most common of these concerns is the worsening state of obsolescence of research instrumentation and facilities in the Nation's research universities. Some suggest that progress now being made in biomedical research may be impeded and the momentum generated by past investments jeopardized.

Three NIH programs are geared directly to the support of research instrumentation: the largest are the Biomedical Research Support Shared Instrumentation Program and the Biomedical Research Technology Program, both administered by the Division of Research Grants. The 1986 estimate for the BRS Shared Instrumentation Program is \$31,828,000, and for the Biomedical Research Technology Program is \$18,504,000.

A study on instrumentation jointly funded by the National Academy of Sciences and the NIH is in its final draft. The study documents the trends in the amount, condition, and cost of existing research instrumentation in the Nation's principal research universities, and the nature and extent of the need for upgrading research instrumentation. The report, not surprisingly, will show a national need for newer equipment in many laboratories, particularly public institutions. The outstanding need seems to center on relatively low cost instruments, perhaps reflecting some degree of success in warding off critical needs for large instruments through the ongoing NIH programs for sharing such instruments. After we have completed an analysis of the survey, we will be able to estimate the cost of restoring our Nation's biomedical laboratory instrumentation to an acceptable level. NIH may well develop alternative strategies both to remedy the current problem and to reduce the likelihood of its recurrence.

For a number of years, the condition of academic research facilities has steadily deteriorated. Federal support in this area has steadily declined. The extent of the need for Federal support of health-related research facilities is difficult to ascertain since no comprehensive assessment of this need has been made since 1968.

NIH is now conducting pilot studies to refine an instrument for survey of the needs and status of the Nation's biomedical research facilities.

Another important but often forgotten element behind medicine's success story is the laboratory animal. During the past century, virtually every major development in biomedical research has depended at some point upon the use of animals.

As you know, scientists and physicians at many institutions are coming under pressure from a small but determined segment of society opposed to this aspect of research. There have been break-ins at about a dozen sites--at other localities, there have been bomb threats and vandalism against the property of investigators and others associated with studies requiring animals.

Legislative activities on the subject at the national, state, and local levels are on the increase. There is a critical need to develop better understanding among the general public, the mass media, and elected officials on the scientific imperatives of using animals in research.

#### The NIH Budget for 1985 and for 1986

Let me turn now to a subject of considerable recent interest--the NIH appropriation--but I make no claim that I will present the final word on the subject.

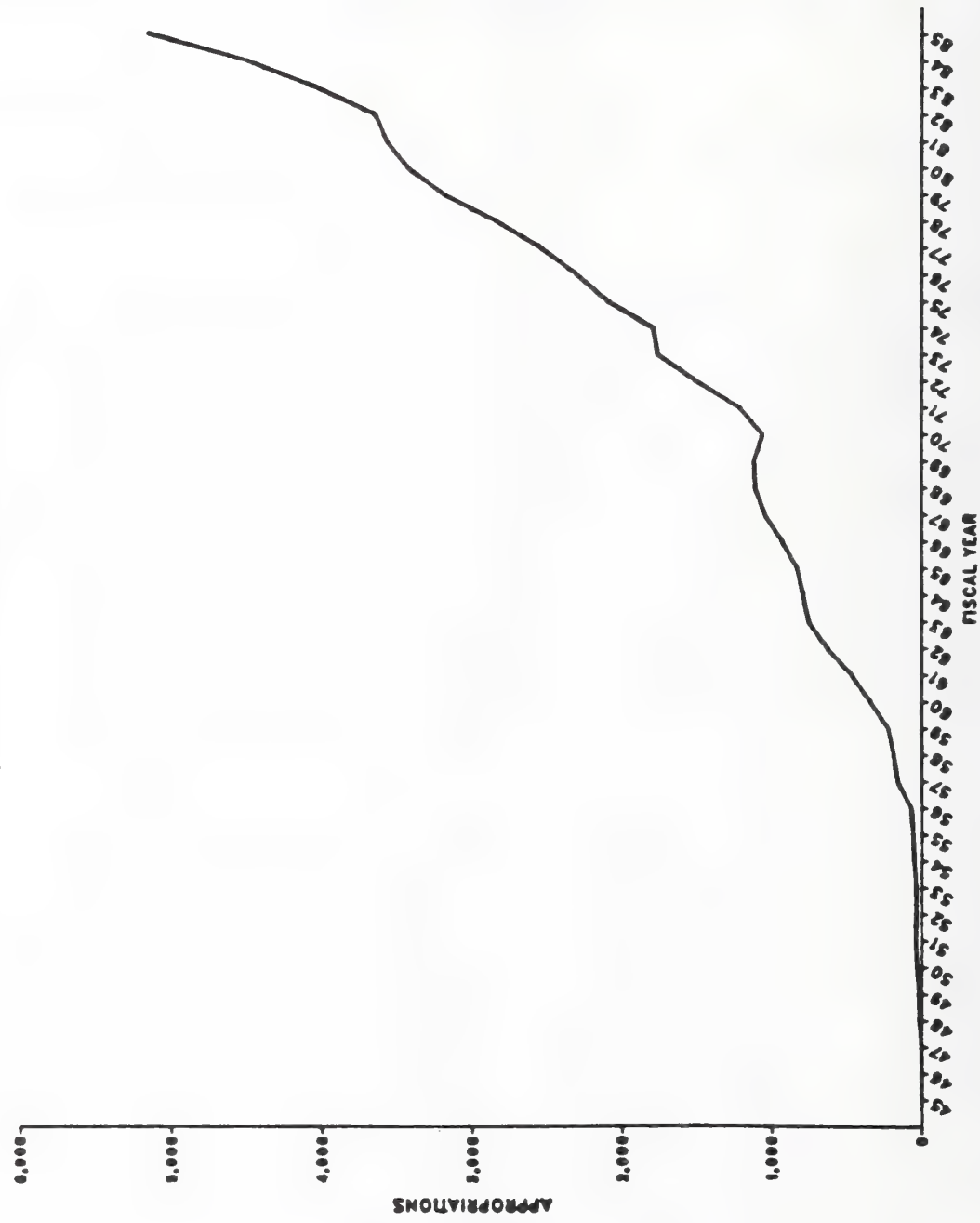
The budget for NIH for Fiscal Year 1985 passed by the Congress and approved by the President was \$5.15 billion dollars. This budget which went into effect with the start of the fiscal year, October 1, provided resources for 6,529 new and competing research project awards. The election on November 4 was widely interpreted as carrying a message to the new Administration to address the deficit by reducing government spending and without increasing taxes. The final touches were put on the FY 1986 budget proposal in late December. At that time, OMB also decided to reduce our allotment of new and competing awards to 5,000 for 1985 and instructed us to use the savings resulting from not funding the additional 1,500 grants for multiyear funding of about 650 awards. Under this plan, only 4,350 of the 5,000 awards made in 1985 would be represented in the commitment base for Fiscal Years 1986 and 1987. A similar ploy was ordered for 33 of the 500 new and competing centers authorized for 1985. These two measures together were calculated to provide a savings of almost a billion dollars in the ensuing fiscal years.

This budgetary rearrangement was designed to provide a stable number of 5,000 new and competing renewal awards in both fiscal years in spite of a reduction in the total NIH budget of \$272 million in 1986. A combination of the original Congressional budget for 1985 and the President's request for NIH for 1986 would otherwise have supported 6,529 new research projects starts one year and only 2,100 the next. The proposed revision of the 1985 budget has occasioned a vigorous negative reaction from the extramural community. Just recently, the Comptroller General has ruled that multiyear funding in the absence of specific Congressional intent is illegal. The Department of Health and Human Services and the OMB are studying the Comptroller General's opinion and are planning to respond to it. In my view, it is highly desirable that this issue be settled quickly, for at present we are holding back substantial amounts of funds in order that we can make multiyear awards if that is the ultimate instruction. Of course, we do not know what Congressional action on

the 1986 budget will be. For the past 15 years at least, Administrations have tended to request modest increases for NIH, since Congress has tended to add to the requested budget. In fact, the figures from 1970 through 1984 show that Administration requests averaged 2.7 percent over the previous year and Congressional action 8.7 percent. At present, Congress is awaiting a budget resolution and will probably coordinate its response to the proposed revision of the 1985 budget with its recommendations for 1986.



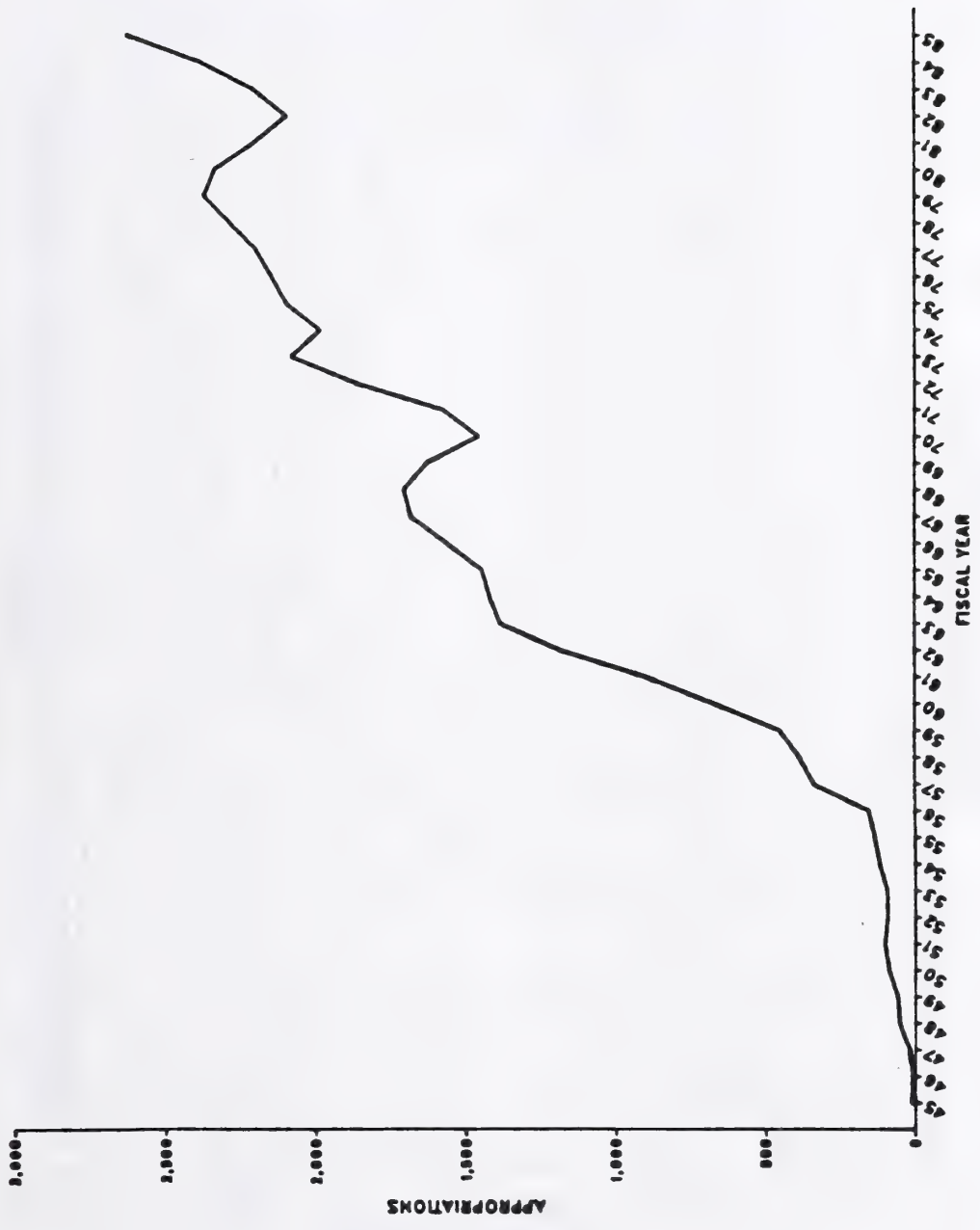
# Total NIH Appropriations in Current Dollars, FY 1945-85 Excluding Programs Transferred Out (Dollars in Millions)



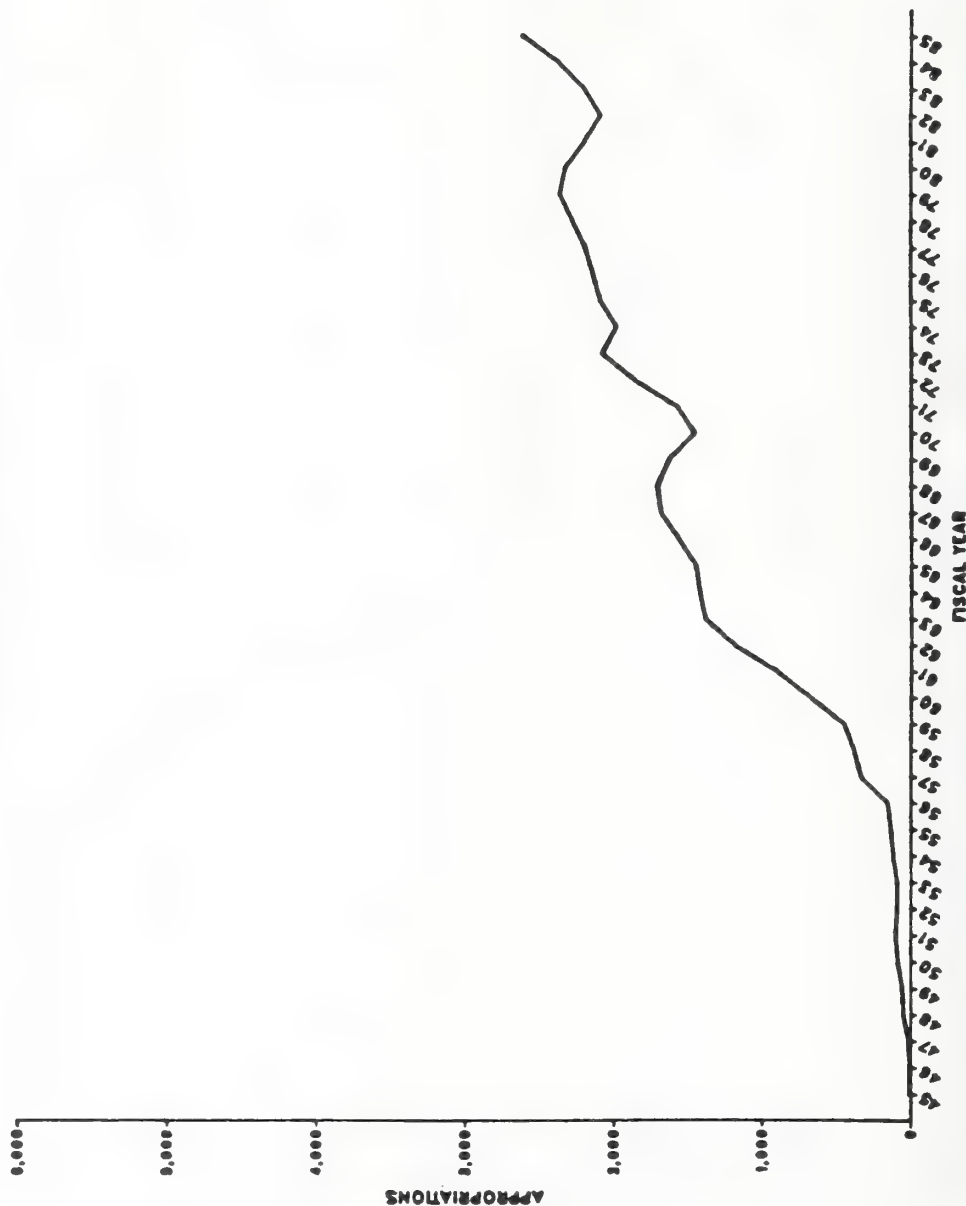
NOTES: TQ excluded. 1985 data preliminary.

PAB/DPA/OPPE/OD, April 1985

# Total NIH Appropriations in Constant (1975) Dollars, FY 1945-85 Excluding Programs Transferred Out (Dollars in Millions)



# Total NIH Appropriations in Constant (1975) Dollars, FY 1945-85 Excluding Programs Transferred Out (Dollars in Millions)

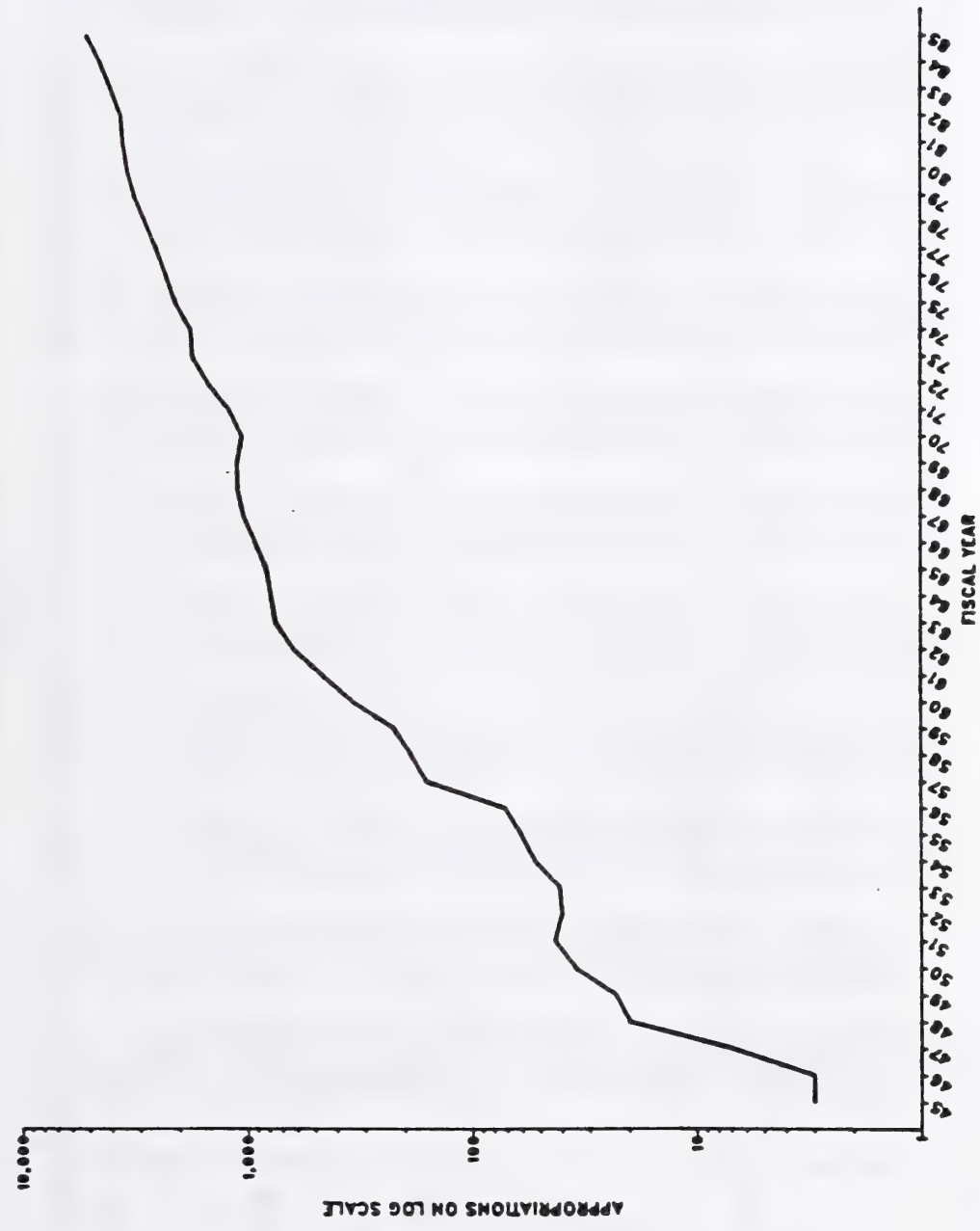


NOTES: Constant dollar conversion uses BRDPI. TQ excluded. 1985 data preliminary.

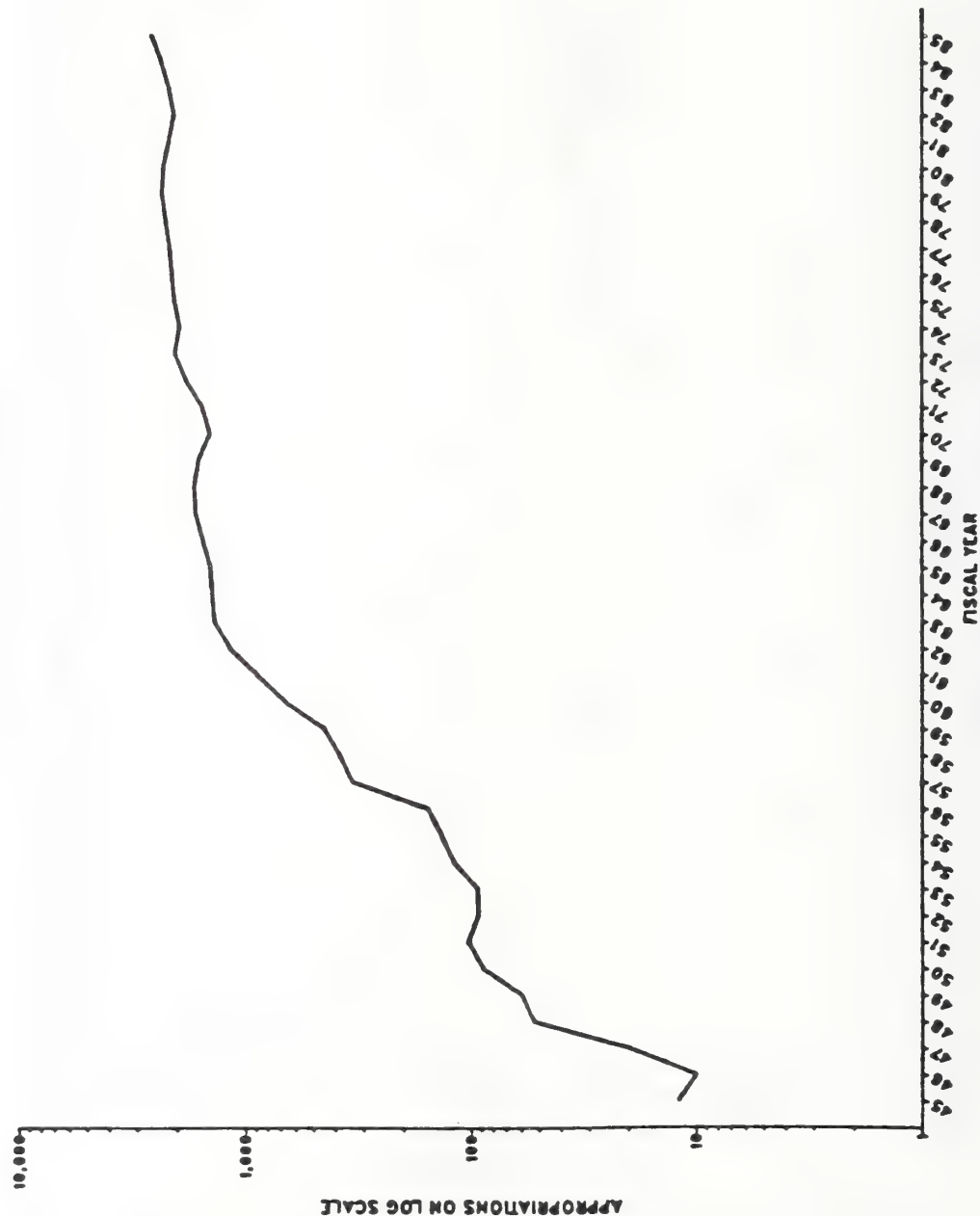
PAB/DPA/OPPE/OD, April 1985



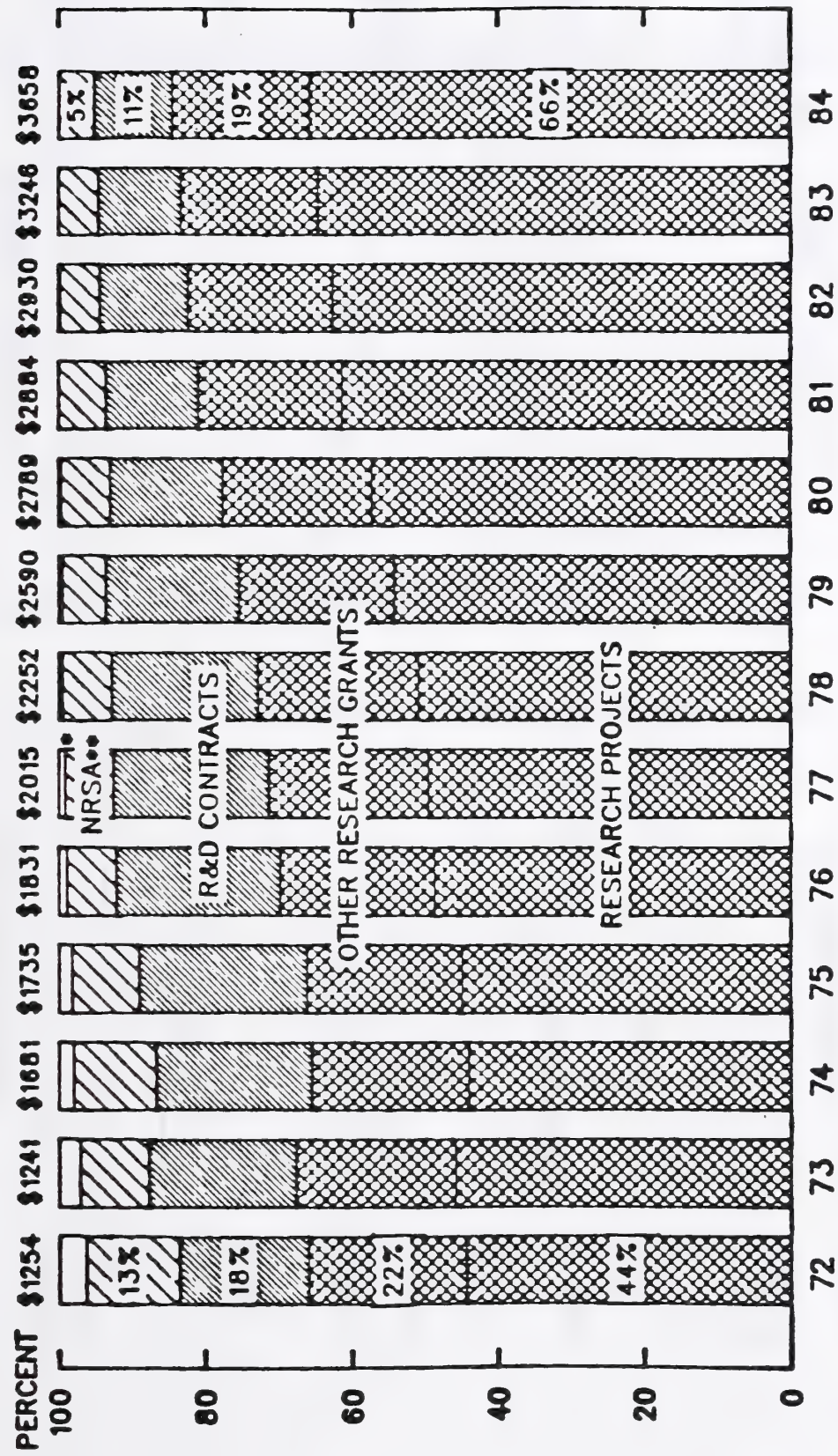
# Total NIH Appropriations in Current Dollars on Log Scale, FY 1945-85 Excluding Programs Transferred Out (Dollars in Millions)



# Total NIH Appropriations in Constant (1975) Dollars on Log Scale, FY 1945-85 Excluding Programs Transferred Out (Dollars in Millions)



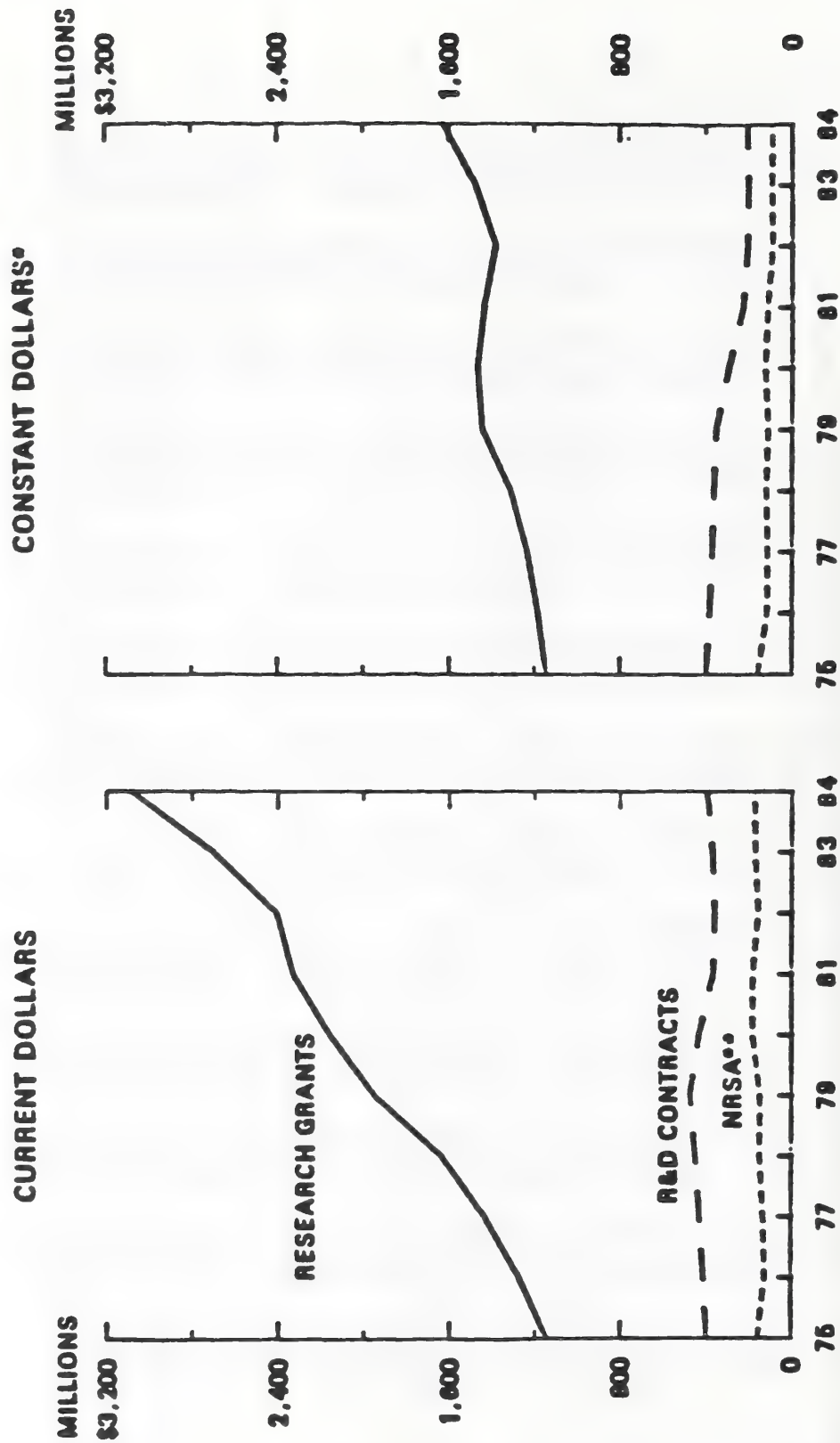
# ALLOCATION OF NIH EXTRAMURAL AWARDS BY ACTIVITY, FISCAL YEARS 1972-1984 PERCENT OF AMOUNT AWARDED (CURRENT DOLLARS IN MILLIONS)



NOTE: EXCLUDES TO. \*INCLUDES CONSTRUCTION AND MEDICAL LIBRARY GRANTS. \*\*INCLUDES PRE-NRSA TRAINING.  
SOURCE: NIH, DRO, STATISTICS AND ANALYSIS BRANCH

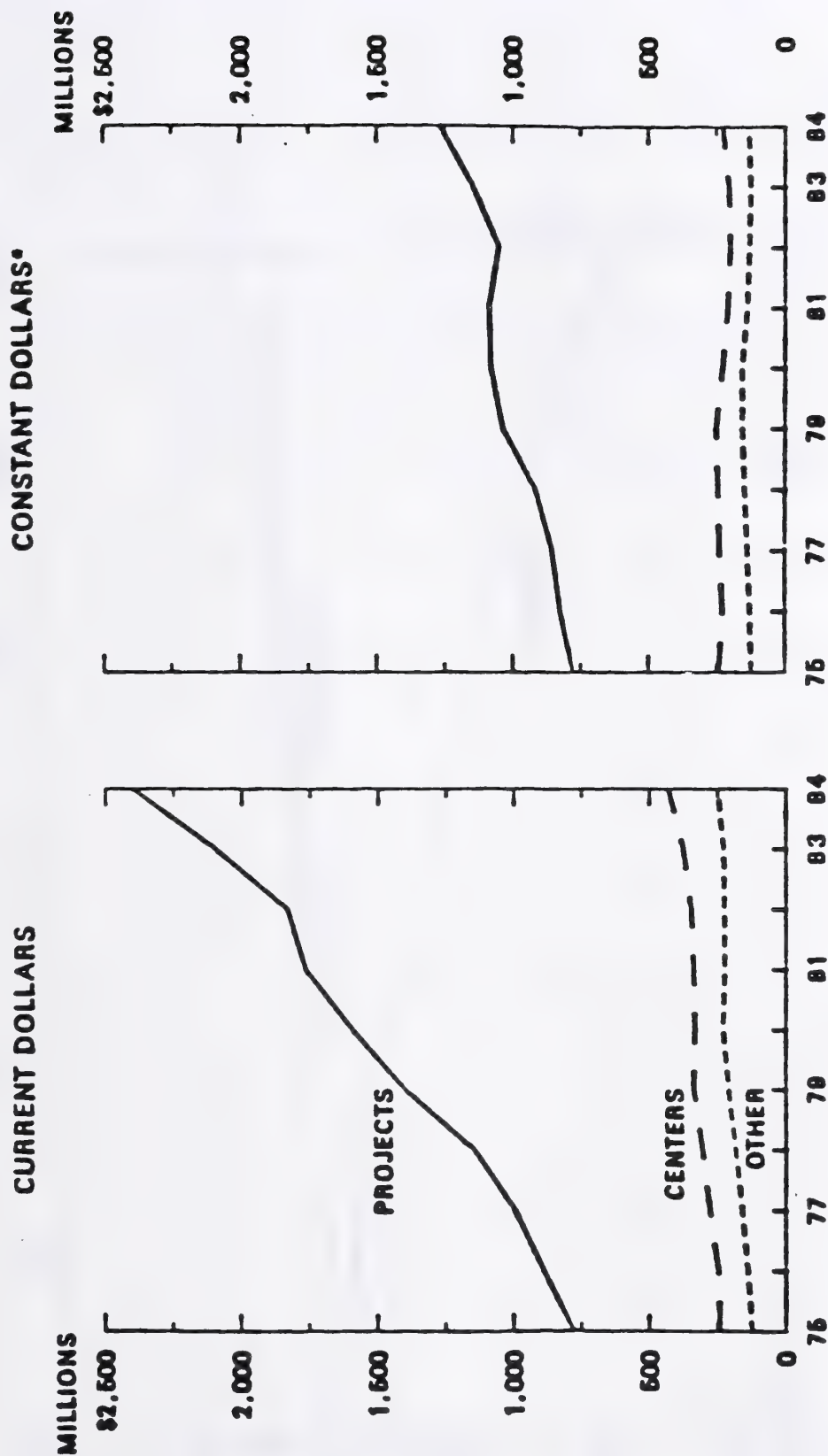


# NIH EXTRAMURAL AWARDS BY ACTIVITY, FISCAL YEARS 1975-1984



NOTE: EXCLUDES IQ.  
 \*BASED ON BIOMEDICAL R&D PRICE INDEX FY1975=100. \*\*INCLUDES PRE-NRSA TRAINING.  
 SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

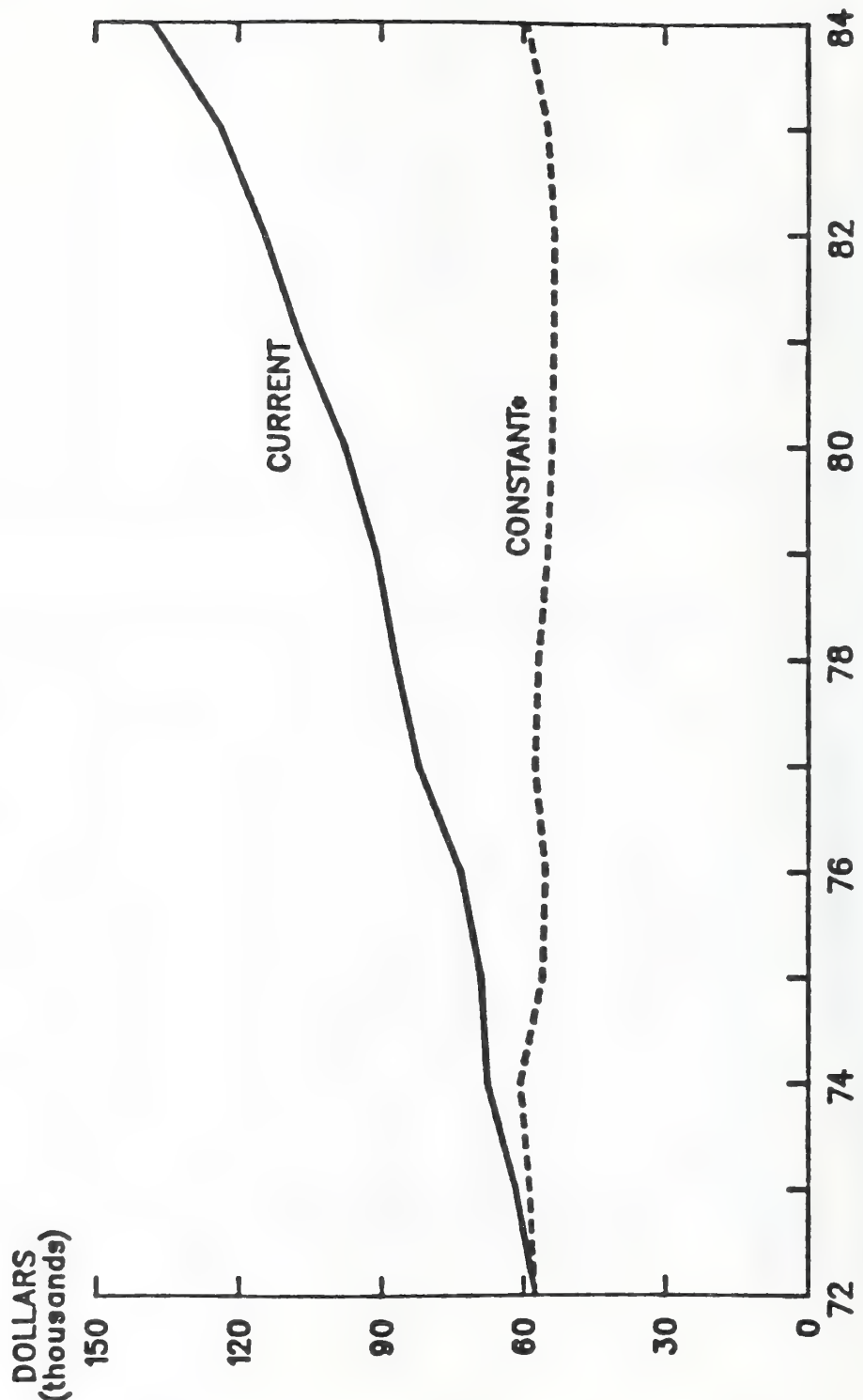
**TOTAL COST AWARDED FOR NIH RESEARCH PROJECT, RESEARCH CENTER,  
AND OTHER RESEARCH GRANTS, FISCAL YEARS 1975-1984**



NOTE: EXCLUDES TO:  
 \*BASED ON BIOMEDICAL R&D PRICE INDEX FY1975=100.  
 SOURCE: NIH, DAG, STATISTICS AND ANALYSIS BRANCH

5.

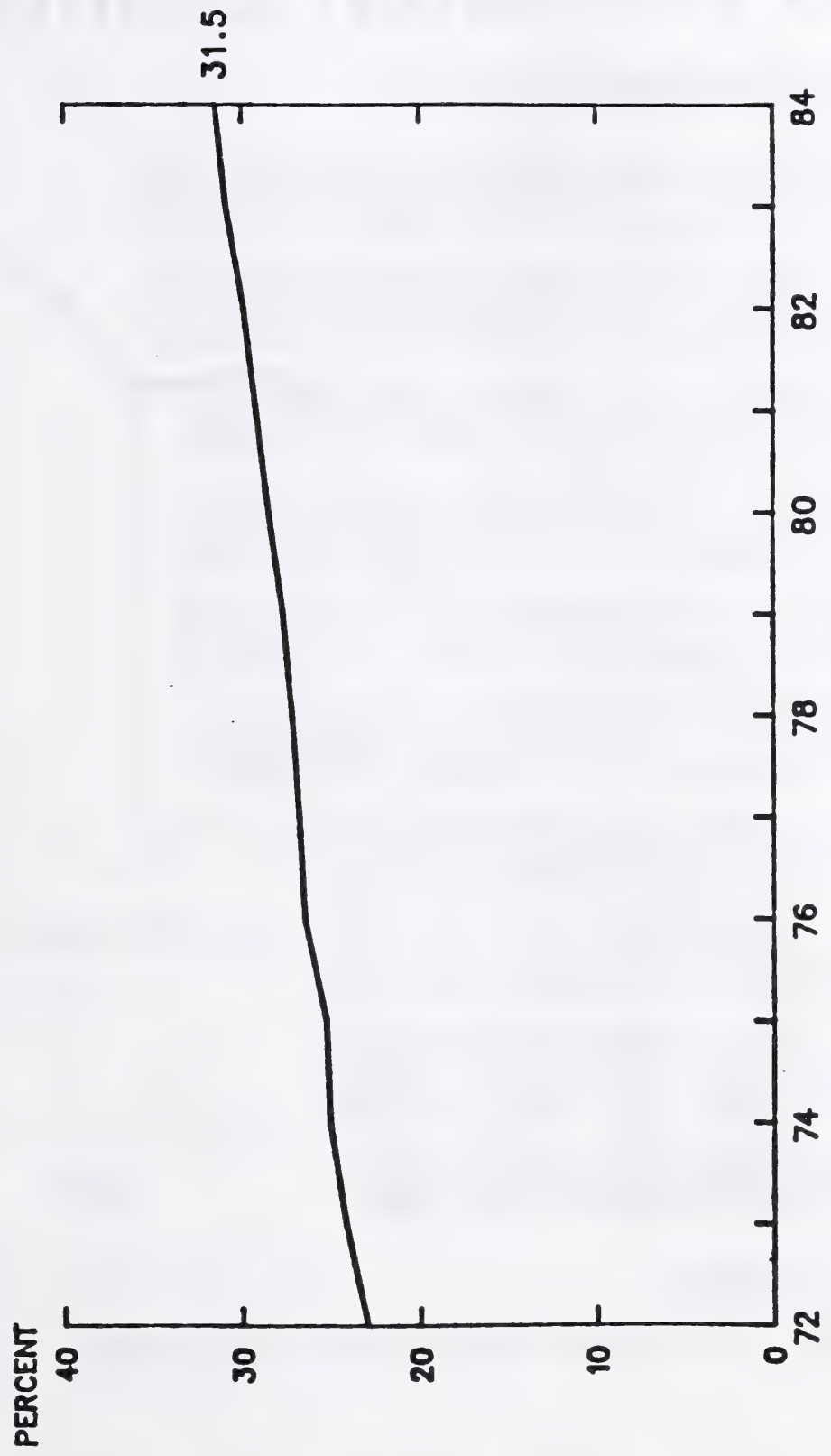
# AVERAGE DOLLARS FOR NIH RESEARCH PROJECT GRANTS FISCAL YEARS 1972-1984



BASED ON BIOMEDICAL R&D PRICE INDEX FY1972-100.  
SOURCE: NIH, DRO, STATISTICS AND ANALYSIS BRANCH

K143  
9/18/86

INDIRECT COST PROPORTION OF TOTAL COST\* FOR NIH RESEARCH GRANTS  
FISCAL YEARS 1972-1984



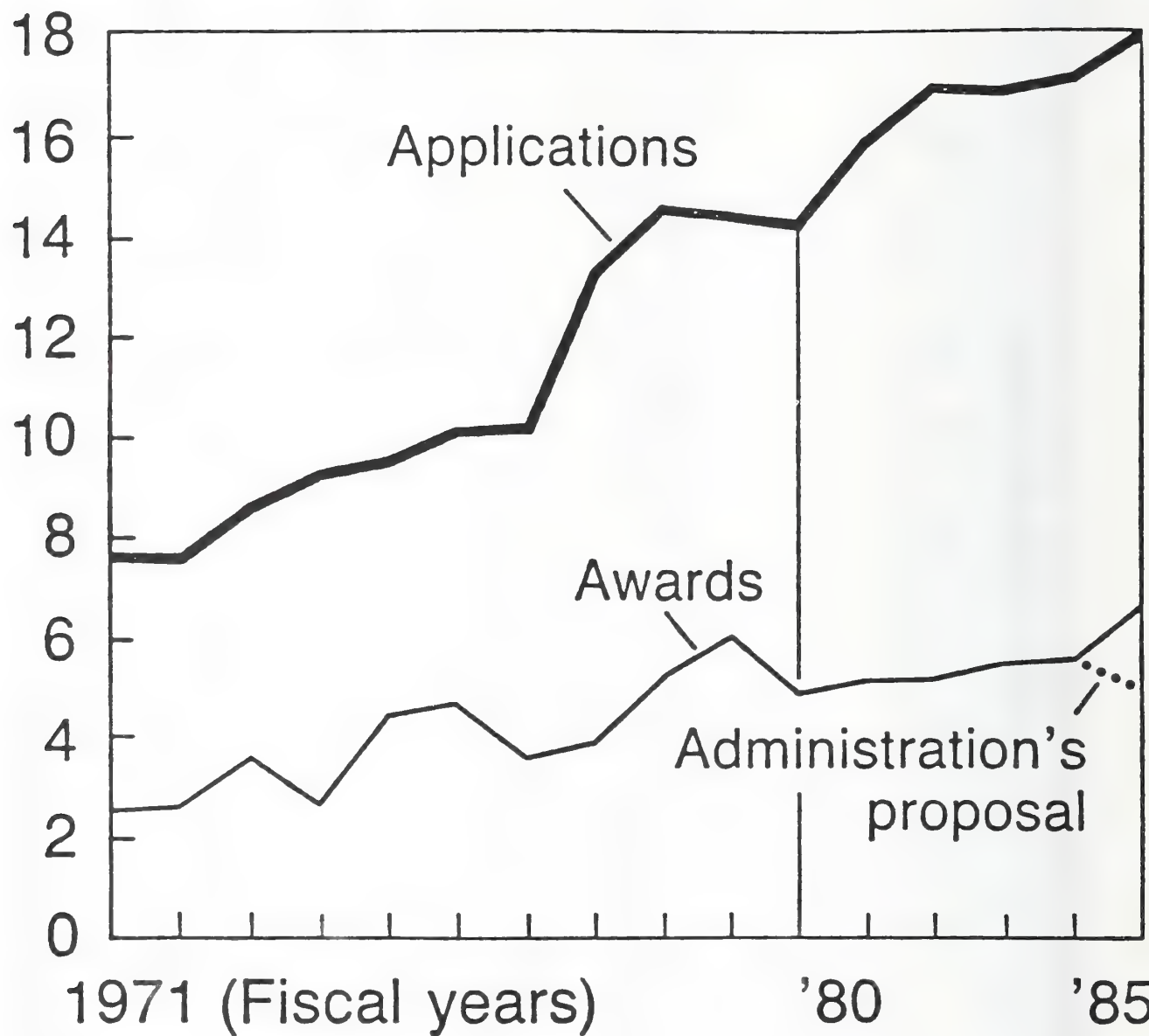
NOTE: \*EXCLUDES DRG, RCP, PAPERS AND JO.  
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

TS4  
4/18/85



17.

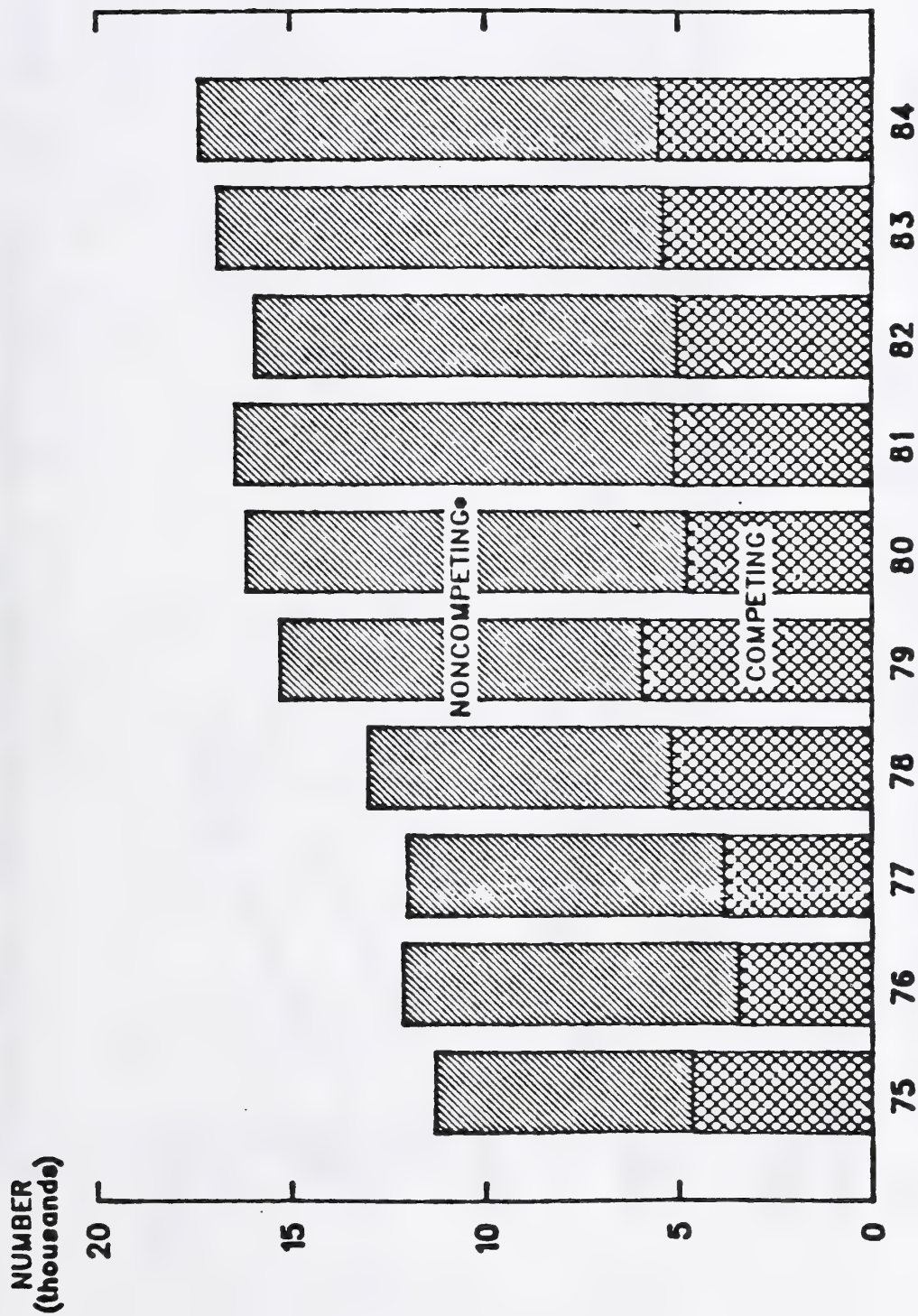
# NIH Research Grants (Thousands)



\*Projected

Source: National Institutes of Health

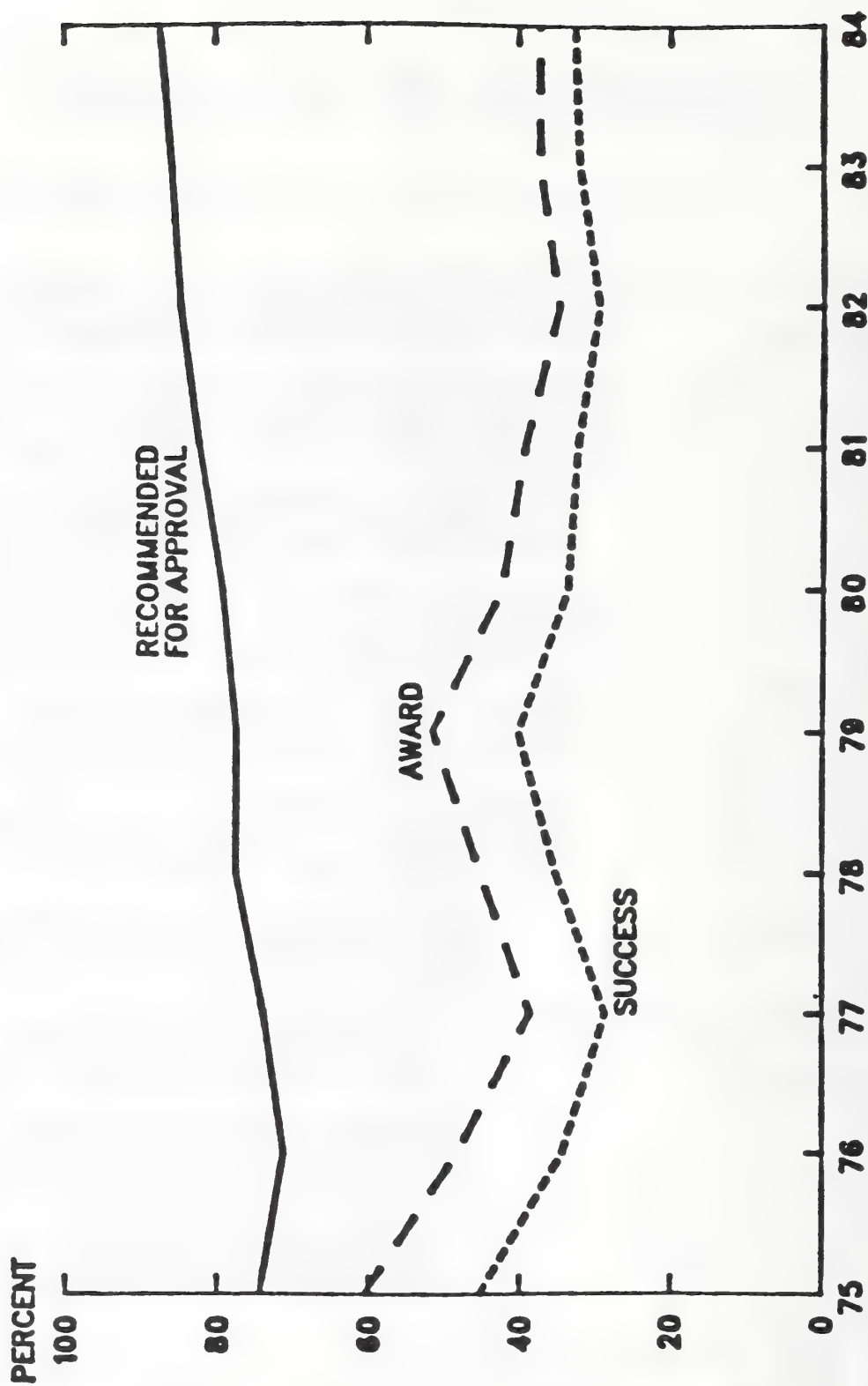
NIH RESEARCH PROJECT AWARDS  
FISCAL YEARS 1975-1984



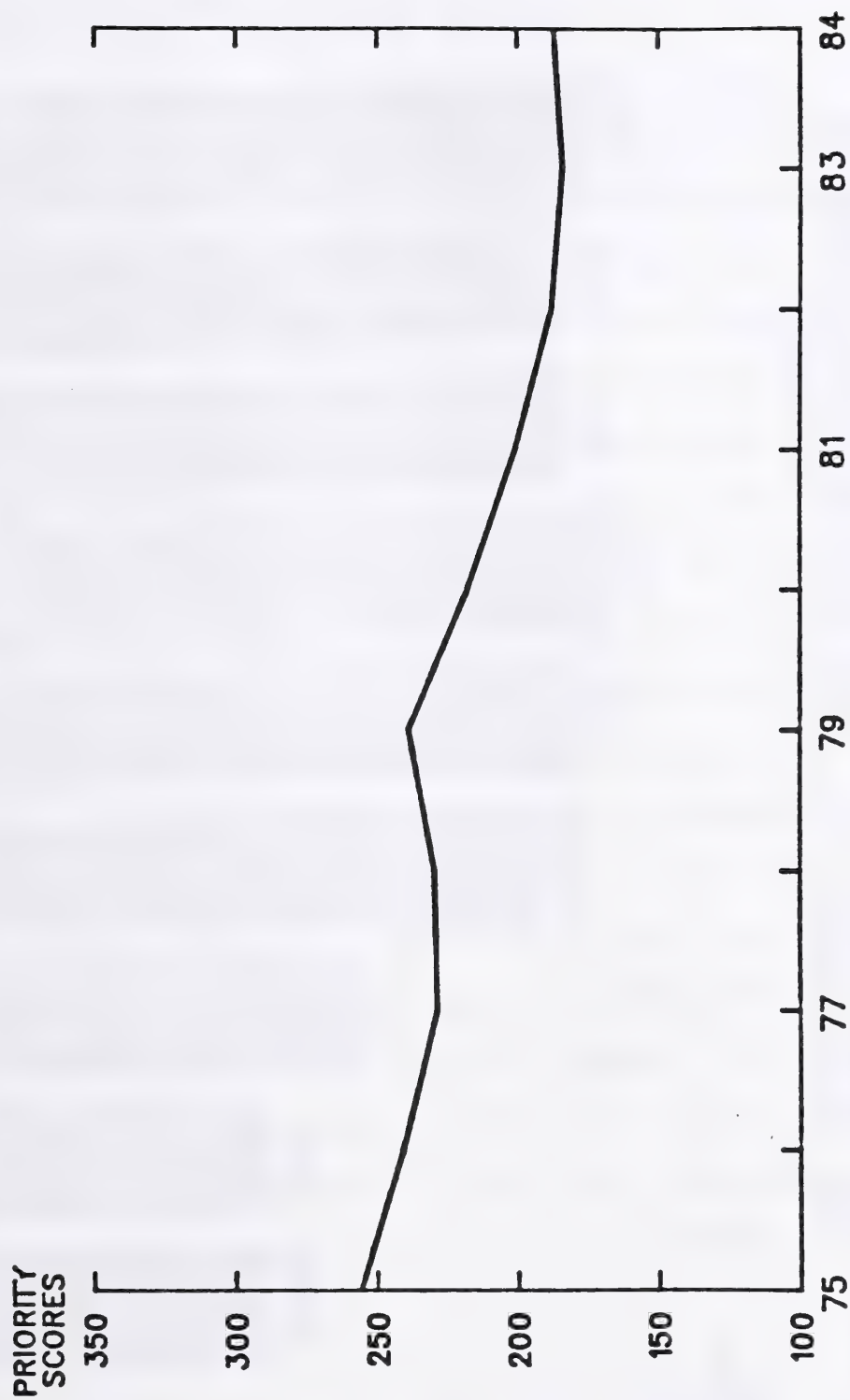
•EXCLUDES SUPPLEMENTS.  
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

8803-JEC001

COUNCIL RECOMMENDED FOR APPROVAL, AWARD, AND SUCCESS RATES  
FOR NUMBER OF NIH RESEARCH PROJECT APPLICATIONS  
FISCAL YEARS 1975-1984



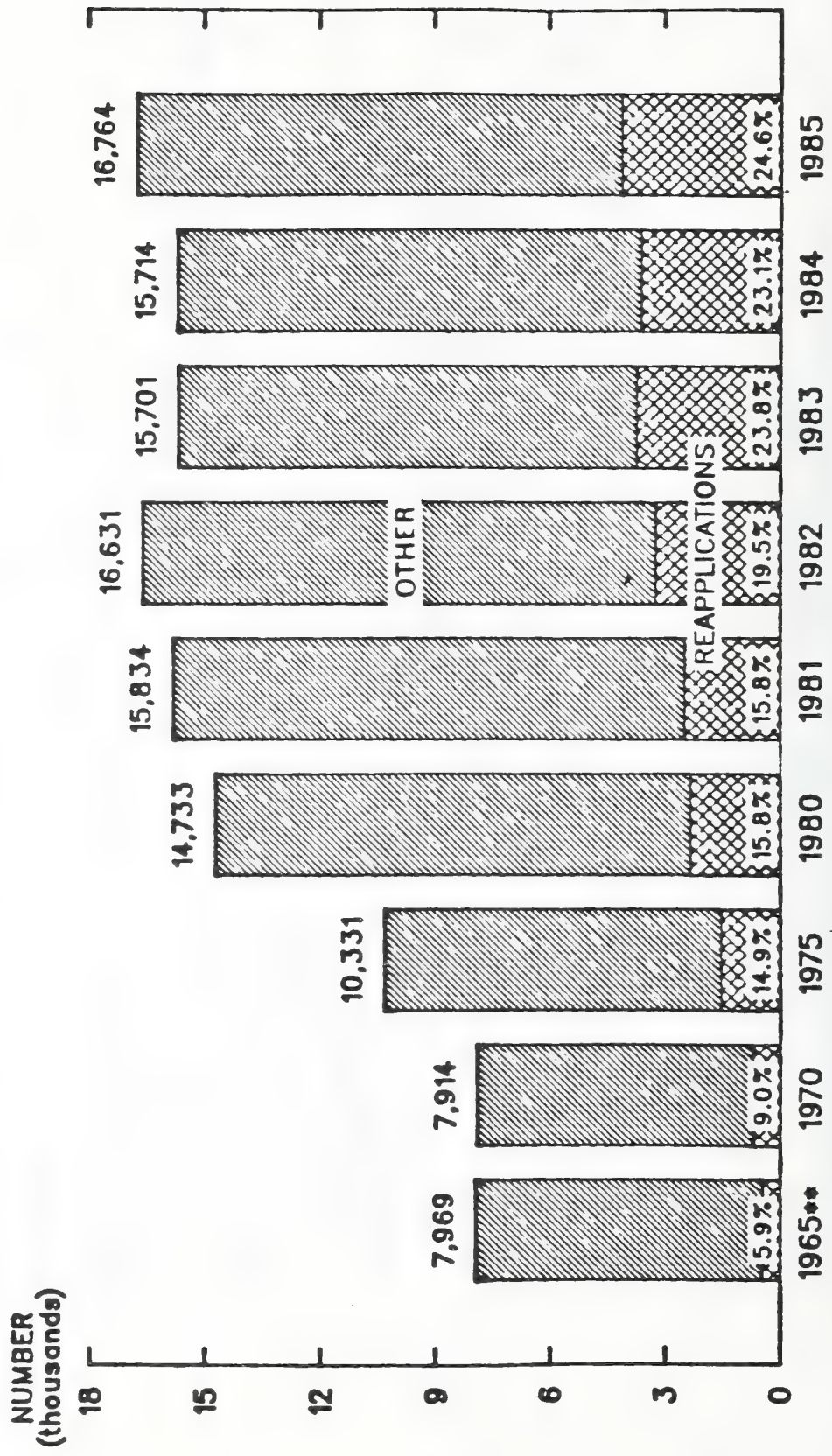
PAYLINES\* FOR NIH COMPETING RESEARCH PROJECT GRANTS  
FISCAL YEARS 1975-1984



NINETY PERCENT OF APPLICATIONS PAID IN A YEAR HAD PRIORITY SCORES BETTER (LOWER)  
THAN THAT SHOWN.  
SOURCE: NIH, DRO, STATISTICS AND ANALYSIS BRANCH



REAPPLICATIONS (AMENDMENTS) AS A PERCENT OF TOTAL COMPETING  
TRADITIONAL RESEARCH PROJECT (R01) APPLICATIONS ASSIGNED TO  
DRG REVIEW GROUPS, SELECTED YEARS 1965-1985\*



\*YEARLY TOTALS BASED ON THREE COUNCIL REVIEW CYCLES. \*\*EXCLUDES NIH AND OTHER NON-NIH DIVISIONS  
(WATER POLLUTION, AIR POLLUTION, ENVIRONMENTAL ENGINEER, ETC.).  
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

## INTRODUCTORY REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

I am pleased to be able to welcome you to this important meeting on behalf of the World Health Organization, the European Medical Research Council, and the National Institutes of Health. This is an exciting time to be a part of any aspect of the development of medicine, but particularly of the growth of biomedical technology assessment. This is an idea whose time has arrived. Far too many drugs, devices, and procedures have been introduced into medical practice without validation of efficacy and safety. Some of them have persisted as medical dogma for decades--a current example is radical mastectomy for carcinoma of the breast. There have, of course, been earlier attempts at assessment. I am reminded, for example, of Osler's Textbook of Medicine in 1893 which was remarkable for its therapeutic nihilism as this great physician characterized most nostrums and remedies in vogue at that time as useless, even dangerous. But those conclusions were reached as informed judgment, not as a result of any systematic organized evaluation. At a time when unprecedented changes are occurring in the tools and practice of medicine, biomedical technology assessment is positioned at the

---

\*Presented at the EMRC Conference on "Methodologies in Technology Assessment," May 21-25, 1985, Copenhagen, Denmark.

\*\*Director, National Institutes of Health, Bethesda, Maryland.

heart of the critical decisions which must be made: decisions on safety and efficacy, timing of introduction and phasing out of technologies, decisions on ethics, legal issues, and cost-benefit aspects. Technology assessment brings together leaders in biomedical research, medicine, government, the health insurance industry, and the public--all the participants in health care--with their unique perspectives. The results of these interactions often have a vital impact on the practice of medicine.

Since the first gathering of the EMRC on this subject, in 1981, major progress has been made in recognizing the importance of technology assessment. Evidence of the emerging prominence of this science can be found in the large number of you who are engaged in this process and the distinction of the panel of speakers we have been able to recruit for this conference, as well as in the publication of a new International Journal of Technology Assessment in Health Care in January 1985, and in the formation of a new society for this purpose only yesterday.

As a science, however, technology assessment is in its infancy. The birth of this new science was made precipitous, and perhaps premature, by the needs which accompanied the recent explosion of new, expensive, and powerful medical technologies. Its growth has been forced by the need to mediate continual adjustments in the health care system, adjustments necessary in order to effect orderly introduction of new modalities and removal of obsolescence in the midst of this technological expansion. Also as in any new science, biomedical technology



assessment has progressed by borrowing from established sciences. In this case, epidemiology, biostatistics, economics, and many other disciplines have made important contributions. As a result, biomedical technology assessment has developed many different faces, depending upon the perspectives of the assessors and the varying needs of the assessments. In government it has been said there are four levels of certainty. The first is fact or truth, second is consensus, third is expert opinion, and fourth and last--when we know nothing about a subject--is policy. This meeting is designed to raise policy at least to the level of consensus.

We who are attending this meeting will have the privilege of assisting this new science in developing its own identity. The nature of our challenge will be to design a common framework for conducting an assessment, while incorporating and preserving some of the soundest and most innovative approaches which are already part of this effort. This common framework will have to define what technology assessment is and specify how it is to be done. It must satisfy the different needs and expectations of those who provide, who pay for, who develop, and who use medical services. And it must enhance the effectiveness of technology assessment, utilizing the most advanced techniques of data collection and synthesis, of decision theory, and of communications and knowledge diffusion.

The presentations you will hear today and tomorrow will come from clinicians, methodologists, behavioral scientists, and many other professionals. As you listen to these stimulating



discussions, I urge you to consider the unique perspective the presenters bring to technology assessment by virtue of their disciplinary affiliations. As we do so, we will be promoting one of the key accomplishments of this gathering: the beginning of a dialogue on the development of biomedical technology assessment which transcends institutional and national boundaries.

Welcoming Remarks\*  
by  
James B. Wyngaarden, M.D.\*\*

Good morning. It is a pleasure to welcome you to this important NIH technology assessment meeting on donor registries for bone marrow transplantation.

As you know, interest in bone marrow transplantation has increased in the past few years in the medical and lay communities. In late 1984, Congress passed legislation asking the Secretary of the Department of Health and Human Services to convene a national conference to explore the feasibility and efficacy of setting up a donor registry for bone marrow transplantation. It is this conference we are opening today. We are pleased to have been given this responsibility and look forward to the sharing of information at this meeting and the drafting of a useful report at its conclusion.

The modern era of human bone marrow transplantation began at the end of the 1960s when techniques of human histocompatibility typing made it possible to select HLA identical siblings as donors. Since then, bone marrow transplantation has been successfully used for therapy of aplastic anemia, severe combined immunodeficiency disease, acute myeloid and other leukemias and for some genetic disorders.

Other applications for bone marrow transplantation may develop. For example, often in cancer therapy hematologic toxicity is dose limiting and the availability of fresh marrow stem cells for such a patient might allow one to deliver high doses of potentially curative therapy to a patient who could not otherwise tolerate such a treatment. Just as the indications for marrow transplantation may expand, we must also realize that there is much research going on relative to other nontransplant therapies for these disorders. Improved chemotherapy for leukemias, for example might obviate the need for marrow transplantation. Processing of marrow donated by a mismatched related donor in order to reduce incompatibility may offer another alternative.

This conference essentially begins, however, with the idea that bone marrow transplantation is currently useful therapy for some disorders, and that the HLA identical sibling donor represents the "gold standard" against which other potential

---

\*Presented at Donor Registries for Bone Marrow Transplantation Conference, Masur Auditorium, NIH, Bethesda, Md., May 13, 1985

\*\*Director, National Institutes of Health

donors should be measured. However, only 25-30% of affected patients will have HL-A identical siblings and for this reason there is obvious interest in identifying other donors if it can be safely done.

Improved knowledge of tissue typing and new methods to combat graft vs. host disease which are under investigation have allowed physicians to expand the donor pool and consider both mismatched family members and matched unrelated individuals as possible marrow donors.

To date there is more experience with the mismatched family member donors than with unrelated donors. The unrelated individuals used as marrow donors have been drawn both from pools of individuals who were typed primarily for use as transfusion donors, or from separate marrow donor files. You will hear the outcome of those experiences during this conference with discussion of specific issues related to the outcome of the transplants and the effects both on donors and recipients.

There are unique legal and ethical issues related to the use of unrelated donors for marrow transplantation. These will also be reviewed and discussed here.

Some of the energy and interest which has led to the convening of this panel has come from people with friends or relatives who might benefit from a marrow transplant and for whom no HL-A identical donor was available. They wish to see such a registry established. As physicians we must concern ourselves with the rights and needs of these recipients but we must also serve as advocates for the rights and needs of the donors.

It is with appreciation of the need for this balanced point of view that NIH has convened this panel to render an opinion as to whether the establishment of a registry of individuals to serve as marrow donors for unrelated recipients is feasible and also whether the establishment of a permanent bone marrow registry of voluntary bone marrow donors at this time is needed and appropriate.

The making of these decisions may well also involve risk-benefit and cost effectiveness considerations, never an easy task at the best of times. The requirement for expertise in all of these areas has led us to have a panel with such wide ranging knowledge. As the panel knows, there is a requirement for implementation within six months of any recommendation they might make.

The NIH has supported much of the research which has led to the advances which are being considered at this meeting. Three Institutes NCI, NHLBI and NIAID have participated actively with the NIH Office of Medical Applications of Research in the planning for and sponsorship of this meeting. I am most grateful to all of you for having come here to share your expertise with us. I wish you good luck in your deliberations.

I would now like to ask Dr. Jacoby, the Acting Director of OMAR to describe the process which we will follow.

## DYER LECTURE - INTRODUCTORY REMARKS BY DR. WYNGAARDEN

I am pleased to welcome you to the annual R.E. Dyer Lecture, a series established in 1950 to honor the late Dr. Rolla Eugene Dyer upon his retirement as Director of the National Institutes of Health.

This honorary lecture series arose from the desire to pay tribute to Dr. Dyer, whose career encompassed 34 years of dedication to the U.S. Public Health Service and to the National Institutes of Health. His work has served as an inspiration for many of us who have followed him. It is thus a special pleasure for me to introduce the speaker for Dr. Dyer's lecture. But first I would like to share with you some highlights of Dr. Dyer's career.

When Dr. Dyer joined the Public Health Service in 1916 he was assigned to field work in bubonic plague. Five years later, in 1921, he came to Washington to the Hygienic Laboratory, which became the National Institute of Health. In 1936 he was appointed director of NIH's Division of Infectious Diseases, now the National Institute of Allergy and Infectious Diseases. He became NIH Director in 1942.

During the early days of his research career, Dr. Dyer's scientific accomplishments in the field of infectious diseases were numerous. Most significant was his work on endemic typhus; after finding the agent in the common rat flea, he showed how it was spread and helped to develop a vaccine to protect against it.

He also studied scarlet fever, influenza, and Rocky Mountain spotted fever, and in 1940 showed that a "new disease" in the United States was in fact "Q" fever, previously found in Australia.



Dr. Dyer was a respected administrator as well as an eminent researcher. Previously unparalleled expansion and change occurred during his 8 years as Director of NIH. In 1948, with the establishment of the National Heart Institute, NIH became the National Institutes of Health. Dr. Dyer was involved in forming several other Institutes and was instrumental in developing the research grants program and in constructing this building, the Clinical Center. When he retired, 35 years ago next October, NIH was well on its way to becoming the world's foremost biomedical research institution.

Because of Dr. Dyer's contributions to NIH, the selection of a speaker for his lecture is made personally by the Director of NIH, with advice from the senior scientific staff. Each Dyer lecturer is an internationally recognized scientist whose contributions to medical and biological knowledge pertain specifically to the problems of infectious diseases.

Tonight's speaker is indeed worthy of this honor. Dr. Louis H. Miller is a world-renowned scientist whose work has significantly advanced our knowledge of malaria.

Dr. Miller received a Bachelor of Science degree from Haverford College in 1956 and his M.D. degree from Washington University in St. Louis in 1960. After completing his residency at Mount Sinai Hospital in New York, he earned a Master's degree at Columbia University and spent a year as a renal metabolism fellow at Cedars-Sinai Medical Center in Los Angeles. He served two years with the U.S. Army Medical Corps at the SEATO Research Laboratory in Thailand. He returned to Columbia in 1967, to join the faculty of the College of Physicians and Surgeons, in

the Department of Tropical Medicine. In 1971 he came to NIH, to head the Malaria Section in the Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases.

Dr. Miller received the NIH Director's Award in 1977 and the Public Health Service Superior Service Award in 1983. Last year, he was elected an Honorary Fellow of the Royal Society of Tropical Medicine and Hygiene. The Federal Republic of Germany recently honored him with the prestigious Paul Erlich-Ludwig Darmstaedter Prize for work aimed at the creation of vaccines against malaria.

Tonight, Dr. Miller will speak to us on "Malaria: Cell Surface Proteins as Receptors and Immunogens."

Dr. Miller.

May 1, 1985



DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH  
NATIONAL LIBRARY OF MEDICINE

BOARD OF REGENTS  
MINUTES OF THE 79TH MEETING  
JUNE 6-7, 1985

BOARD ROOM  
NATIONAL LIBRARY OF MEDICINE  
BETHESDA, MARYLAND



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE

THE BOARD OF REGENTS OF THE NATIONAL LIBRARY OF MEDICINE

Minutes of Meeting 1/ 2/  
June 6-7, 1985

The Board of Regents of the National Library of Medicine was convened for its seventy-ninth meeting at 9:00 a.m. on Thursday, June 6, 1985, in the Board Room of the National Library of Medicine, Bethesda, Maryland. Dr. L. Thompson Bowles, Chairman of the Board of Regents and Dean for Academic Affairs and Professor of Surgery, The George Washington University Medical Center, presided. In accordance with P.L. 92-463 and the Determination of the Director, NIH, and as announced in the Federal Register on April 24, 1985, the meeting was open to the public from 9:00 to 4:30 p.m. on June 6 and from 8:30 to 9:20 a.m. on June 7. The meeting was closed from 9:20 to adjournment at 11:30 a.m. on June 7 for the review, discussion, and evaluation of grant applications. A Board roster is enclosed under Attachment A.

Board members present were:

Dr. L. Thompson Bowles  
Dr. Lois E. DeBakey  
Mrs. Shirley Echelman  
Mr. Russell L. Fenwick  
Dr. Albert E. Gunn  
Dr. David T. Kingsbury (Ex officio)(June 6)  
Mr. John Lopez  
Dr. David O. Moline  
Dr. Grant V. Rodkey  
Dr. Eugene A. Stead, Jr.

Alternates to ex officio members present were:

Dr. Faye G. Abdellah, representing Dr. C. Everett Koop.  
Brig. Gen. Thomas P. Ball, Jr., USAF, MC, representing Lt. Gen. Max B. Bralliar.  
Capt. Noel Dysart, representing Vice Admiral Lewis H. Seaton.  
Mr. James M. Hahn, representing Dr. John W. Ditzler.  
Dr. Robert Rabin, representing Dr. David T. Kingsbury (June 7).  
Mr. William J. Welsh, representing Dr. Daniel J. Boorstin.

Unable to attend:

Col. James E. Hastings

---

1/For the record, it is noted that members absent themselves from the meeting when the Board is discussing applications from their respective institutions (interpreted to mean the entire system of which a member's institution is a part) or in which a conflict of interest might occur. Only when an application is under individual discussion will the Board member absent himself. This procedure does not apply to "en bloc" actions.

2/The Board of Regents, when considering the extramural programs of NLM, also constitutes and serves as the National Medical Libraries Assistance Advisory Board.

National Library of Medicine staff members attending this meeting included:

Dr. Donald A. B. Lindberg, Director  
Dr. Harold M. Schoolman, Deputy Director for Research and Education  
Mr. John Anderson, Director, Information Systems, OD  
Dr. Jeanne Brand, Chief, International Programs Branch, EP  
Mr. Arthur J. Broering, Deputy Associate Director for Extramural Programs  
Mr. Kenneth Carney, Executive Officer, OD  
Ms. Lois Ann Colaianni, Associate Director for Library Operations  
Dr. William G. Cooper, Associate Director for Extramural Programs  
Dr. Roger W. Dahlen, Chief, Biomedical Information Support Branch, EP  
Mr. B. Earl Henderson, Acting Director, Lister Hill National Center for Biomedical Communications  
Ms. Betsy L. Humphreys, Deputy Associate Director for Library Operations  
Dr. Henry M. Kissman, Associate Director for Specialized Information Services  
Mr. Sheldon Kotzin, Chief, Bibliographic Services Division, LO  
Ms. Eve-Marie Lacroix, Chief, Reference Services Division, LO  
Mr. Robert B. Mehnert, Chief, Office of Inquiries and Publications Management, OD  
Mr. Stanley J. Phillips, Deputy Executive Officer, OD  
Dr. Henry Riecken, Associate Director for Planning and Evaluation  
Mr. Arthur Robinson, EEO Coordinator  
Mr. Mark J. Rotariu, Chief, Office of Financial Management, OD  
Dr. Elliot R. Siegel, Special Assistant for Operations Research, OD  
Mr. Richard T. West, Chief, Office of Program Planning and Evaluation, EP

Others present included:

Dr. J. E. Rall, Deputy Director for Intramural Research, NIH  
Ms. Grace McDonald, Extramural Associate, NIH  
Ms. Ileen E. Stewart, Executive Secretary, Special Study Section, DRG, NIH

Members of the public present:

Mr. Ken Burgess, President, DataSpan, Orchard Park, New York  
Mr. Thaddeus Plante, Legal Assistant, Kaye, Scholar, Fierman, Hays & Handler  
Mr. Dan Triscari, National Sales Manager, DataSpan, Orchard Park, New York  
Ms. Patricia Williams, Reporter, "The Blue Sheet"

## I. OPENING REMARKS

Dr. L. Thompson Bowles, Chairman, welcomed the Regents and guests to the 79th meeting of the Board of Regents. He recognized a new ex officio member: Brigadier General Thomas P. Ball, Jr., Commander of the Malcolm Grow Medical Center at Andrews Air Force Base.

Dr. Bowles noted that the Library is continuing to operate in a "fascinating" Federal budgetary environment, unique to his knowledge. There is much budget negotiating taking place in the House and Senate, and it will be some time before we know exactly what the 1986 budget will contain. He also commented about the evolving interest in medical informatics and information management as applied to biological science and clinical practice. Greater and greater importance is being attached to this newly recognized field of endeavor. He and Dr. Lindberg participated in a well-attended conference on medical informatics sponsored by NLM and conducted by the Association of American Medical Colleges. Dr. Bowles concluded his opening remarks by emphasizing the importance of the discussion that would take place later in the day about the role of the Regents in NLM's long-range planning.

## II. REMARKS OF THE NIH DEPUTY DIRECTOR FOR INTRAMURAL RESEARCH

Dr. J. E. Rall noted that the primary role of the Library as a collector and disseminator of biomedical information is enshrined in item one of Section 301 of the Public Health Service Act--the basic legislative authority for the National Institutes of Health. He reminisced about how literature searching by scientists has changed for the better over the last two decades, primarily as a result of services introduced by NLM. He said he hoped that the Library would be as successful in addressing the problems and opportunities of the future, and he cited NLM's plans in developing a unified medical language as one important component of this future. Dr. Rall commented briefly on the current status of budget and legislative matters affecting NIH. It was his assessment that a "reasonable" level of funding was in prospect for both NIH and NLM. H.R. 2409, introduced by Representatives Waxman and Madigan, would create two new institutes at NIH (for arthritis and nursing); a similar bill last year was vetoed by the President. The bill would authorize two new ex officio Regents for the Library: the Director of the National Agricultural Library and the Dean of the Uniformed Services University for the Health Sciences. He concluded his remarks by thanking the Regents for their support of the Library.

## III. CONSIDERATION OF MINUTES OF PREVIOUS MEETING

The minutes of the January 24-25, 1985, meeting were amended by the substitution of "NIH-sponsored" for "NLM-sponsored" on page 10, paragraph 2, line 18, and unanimously approved.

## IV. DATES OF FUTURE MEETINGS

The Board will meet next on September 17-18 (Tuesday-Wednesday), 1985. The dates of February 6-7 were confirmed for the winter meeting. The dates of June 5-6 were selected for next spring's meeting.



## V. REPORT OF THE DIRECTOR, NLM

Dr. Donald A. B. Lindberg discussed the NLM budget situation--the President's FY 1986 budget contains \$53,320,000 for NLM, down from the FY 1985 operating level of \$55,848,000. Budget reductions will of necessity come primarily out of Library Operations, Dr. Lindberg said, with lower spending for acquisitions, processing, and publications. There is a counterview to the Administration's 1986 health budget that has been prepared by the Ad Hoc Group for Medical Research Funding. This group favors an increase of \$12,000,000 for NLM in 1986. Also testifying for an increase for the Library was the Medical Library Association, the Association of Academic Health Science Library Directors, and the American College of Medical Informatics, all of which have suggested an increase of about \$12,000,000. Dr. Michael DeBakey testified for a similar increase and drew attention to the distinguished record of the Library.

The House and Senate hearings were friendly and favorable to NLM, Dr. Lindberg said, with a number of penetrating questions being asked about IAIMS, the need for a unified medical language, and MEDLARS pricing. The bill currently before the Congress would reauthorize the Medical Library Assistance Act at the level of \$12,000,000; this would be a satisfactory level. Also, on the legislative front, Dr. Lindberg noted that Rep. Torricelli has reintroduced his bill about animal welfare; this proposed legislation would have a profound effect on the Library.

The Director announced several staff appointments: Duane Arenales, Chief of the Technical Services Division, and Eve-Marie Lacroix, Chief of the Reference Services Division. There have been several sabbatical appointments from the academic world: Dr. Dennis Fryback from the University of Wisconsin, doing research on decision-making at the Lister Hill Center; Dr. Yohannes Yesus from the University of Missouri, doing research on expert systems; Dr. Thomas Hall from Washington University, doing historical research at NLM; and Dr. Walter Holland, an NLM Fogarty Fellow from Oxford University. Dr. John Starkweather of the University of California at San Francisco will be coming on sabbatical to NLM in September 1985.

Dr. Lindberg noted several brief items about NLM information systems. (1) He lauded the Library's computer operations staff for making NLM's online databases available essentially 24 hours a day beginning June 1. (2) DOCLINE, an online service for transmitting interlibrary loan requests, became operational this spring. There was great enthusiasm for DOCLINE at the recent Medical Library Association meeting. (3) NLM is working to improve the "front end" of MEDLINE to simplify access for inexperienced users. (4) The commercial sector has been informed that NLM is willing to provide documentation of the MEDLARS retrieval software to companies that may wish to develop optimal user "front-end" interfaces for their clients. (5) There are a number of companies with whom NLM is cooperating to experiment with putting NLM online databases on videodisc. (6) By the next Board meeting there will be one or two new commercial vendors of MEDLINE. (7) NLM has started the long process of describing and justifying future computer requirements and soliciting approval for new hardware.

There is a proposed new Office of Management and Budget circular concerning Federal information management policy. It contains a section that would require Federal agencies, before offering an information product or service, to consider whether it is reasonable to expect that another organization, public or private,



would offer such a product or service if the agency did not. "If so, then the agency should not disseminate the information product or service." NLM, NIH, and such organizations as the Association of Research Libraries and the American College of Physicians have offered comments to OMB objecting to this section (among others) of the proposed policy. Dr. Lindberg sent a letter to the Office of Management and Budget on May 10 expressing his concerns about the circular. Later in the meeting, Dr. Rodkey moved that the Board formally endorse the letter, and this motion was passed unanimously.

At the Director's request, Dr. Harold Schoolman elaborated on the Symposium on Medical Informatics: Medical Education in the Information Age, held on March 7-8 at the Association of American Medical Colleges and alluded to earlier by the Chairman. The Symposium will result in a report on the state of the art in medical informatics that identifies problems in the field and makes recommendations on how the academic community should respond. The Steering Committee that is writing the report includes a number of well-known figures in the medical informatics field. A first draft of the report will be ready in about three months; final publication is expected in March 1986.

Dr. Lindberg concluded his report by mentioning briefly recent activities to form a "Friends of the Library" group; a workshop on artificial intelligence being hosted by NLM in July; the visit earlier this year by Dr. Frank Young, FDA Commissioner; and encouraging discussions with representatives of the American Medical Association about collaborating to develop a unified medical language.

Following the Director's report, there was extensive discussion about the implications of the proposed OMB Federal information policy circular. Mrs. Echelman described the activities of the Association of Research Libraries (ARL) in gathering the comments of other organizations to present them to the OMB. She distributed to the Regents the formal ARL response to the proposed policy. It is her opinion that the OMB circular is "one of the most dangerous documents to come out of a U.S. Federal agency since the Alien and Sedition Act which was adopted by Congress in 1798." She said that the policy will limit severely the availability of information of all kinds from the Federal government. The scientific community, she continued, should be made aware what it would mean to the dissemination not only of research information, but also of clinical information. It may also have a profound impact on the private sector--information heretofore provided to companies by government agencies may no longer be available to them. Several of the Regents suggested that the health community should not be too global in its objections, but should narrow its arguments to those that are pertinent to biomedicine. Mr. Welsh pointed out that there are some members of Congress who agree with the thrust of the circular and that their point of view should be considered before health organizations formulate their response. Mr. Lopez added that another aspect of the controversy is the wide concern these days for the transfer of valuable technological information to other countries.

## VI. MEDICALELECTROGRAPHIC PROGRAMS

Mr. John K. Lopez, Executive Vice President of Medicalectrographic Instrumentation, Inc. (MEGI), and a member of the Board of Regents, described the innovative systems and services developed by that firm in the area of onsite diagnostic and patient management services by medical specialists. This is done through telephonic and/or satellite transmission of patient information, including

electrocardiographic (EKG), electroencephalographic (EEG), electroradiographic x-ray and image (ERG), and electropathographic (EPG) data. Mr. Lopez showed the Regents a suitcase-size, full-scale model of the satellite antenna used; the other equipment required was also quite portable, totaling 42 pounds. Aided by his colleagues, Mr. Dan Triscari and Mr. Ken Burgess, he demonstrated the "live" transmission of several high-quality radiographic images by satellite to the Mayo Clinic and back to NLM (speed: 9600 baud; resolution: 512 x 512). The system is designed to allow specialists to receive accurate images and data from remotely located patients, thus enabling the specialist to render a diagnosis without actually "seeing" first-hand the x-rays (or other images) or the patient. Because the system can use satellite communications, it also has great potential in lesser-developed countries where land-based telephone communication is unreliable or lacking altogether. The extreme ease of use of the system will also facilitate its use by untrained personnel.

## VII. NLM LONG-RANGE PLAN

Dr. Henry Riecken, NLM Associate Director for Planning and Evaluation, reported on recent developments in NLM's planning. He emphasized three aspects: a planning model has been evolved; a planning process has been structured; and NLM senior staff have become actively involved in the planning operation. The evolution of the planning model was facilitated by several groups of consultants earlier this year. The model employs the concept of a 20-year goal which is not absolutely clear, that is, a "fuzzy goal." In the 10-year range there are what Dr. Riecken called "windows of opportunity"--sets of circumstances (legal, technological, economic, etc.) that allow one to make progress toward the fuzzy goal. A set of "impediments" also lurks in the 10-year range. The planning model requires that these windows and impediments be identified and that steps be taken so that within the next three to five years, progress toward these windows is facilitated and the removal of the impediments is begun. These steps, which must be undertaken within the three to five year range, are the initiatives that NLM will ask its planning panels to suggest.

The second aspect, the structure of the planning process, involves the development of a taxonomy of medical information activities and five panels of experts to help guide the process. The five information domains around which panels are organized are: building and organizing the Library's collection; locating and gaining access to medical and scientific literature; obtaining factual information from databases; research in medical informatics; and assisting health professions education through information technology. Dr. Riecken noted that NLM staff will not be appointed to membership on the panels, although their views will be represented in background papers given to the panels, and they may be called on as resource persons.

In discussing the third aspect--staff involvement--Dr. Riecken described the successful retreat of NLM senior staff on May 13-14 to discuss planning. The Director had presented his vision of NLM's fuzzy goal at the retreat and, using viewgraphs, Dr. Lindberg briefly described the goal to the Regents. He did this by contrasting NLM's goal as it might have been stated in 1965--including elements of rapid bibliographic retrieval, rapid interlibrary loan, network sharing of collection resources, and so forth. He identified several windows of opportunity and impediments that would have presented themselves. Today, he



said, we can hypothesize a fuzzy goal looking toward 2005 that posits: (1) All U.S. biomedical professionals should have computerized access to practice-linked information--citations, abstracts, full text, teaching/testing programs, expert consultant systems, and raw data appendicial files. (2) Patients shall have the right to choose the service that stores and maintains their medical records, including the possibility that they be part of IAIMS arrangements. (3) There will be a substantial cadre of well-trained library, information, and medical specialists. Windows of opportunity will involve informatics training, Dr. Lindberg said, and also automated indexing, a unified medical language, greater computational capability, health planning (lifetime costing of care), and needed legislation. He noted that for all practical purposes, if you are talking about applying a device or technique in the five to seven year range, it either exists right now (perhaps in a laboratory) or it will not be available at all.

Dr. Lindberg asked what NLM should be doing now to take advantage of those windows. Linking the literature of biomedical research with medical practice is one area. NLM has embarked on a unified medical language project; a standard abstract system planned by NLM could be a part of this. Also important is research on evaluating knowledge representation to support medical decision-making. Strengthening the NLM collection and developing linkages with other information sources are other actions that will facilitate taking advantage of the windows.

Dr. Riecken continued by mentioning a matter that was discussed in yesterday's meeting of the Board of Regents' Working Group on Long-Range Planning: the respective roles of the Regents, NLM staff, and outside advisors. He suggested that the Regents might discuss the advisability of the current membership serving on planning panels, and the desirability of not constraining panels to plan within the framework of current Board policy. He said the next steps are to appoint people to chair the five panels, compose the panels, provide them with any necessary background materials, convene the panels in a series of meetings leading to the preparation and review of a draft plan, and present the plan to the Regents at the June 1986 Board meeting.

Following Dr. Riecken's presentation, Dr. Bowles commented that there is no more important responsibility for the Board and for the Library than to plan for the future. Although he believes that the Regents should play an active role in the planning, he has misgivings about the Regents serving as active voting members on the individual panels of experts. This would lead to an awkward conflict of interest as Regents participate actively in developing parts of the plan and then, one year from now, take part in the discussion of and voting on the entire long-range plan. He was not suggesting that the Regents be excluded from the panels--they might serve as resources or consultants--but that they not be full voting members. He also asked that the Regents suggest names of people who might serve on the panels; the names will be needed by Dr. Riecken within two weeks. He also remarked that it would be unwise to prevent planning panels from questioning current Board policies and felt we should allow panelists a broad range in thinking about the future. There was discussion following Dr. Bowles' comments about the role of the Regents in the planning and about the composition of the panels. A motion was passed unanimously to accept the general outline of the planning process as presented by Dr. Riecken, with the goal of presenting to the Regents a draft plan in June 1986.

## VIII. UPDATE ON PUBLIC INFORMATION ACTIVITIES

Mr. Robert Mehnert, Chief of the NLM Office of Inquiries and Publications Management, reported on progress in planning NLM's education/outreach program. This is a subject in which the Regents have shown great interest over the past year. The interest is prompted by the belief that, if the Library is to make maximum contribution to society, its services need to be better known to the scientific community. To bring this about, the Board Chairman in May 1984 appointed a Board of Regents' Task Force on Public Affairs. The Task Force presented its report at the last meeting of the Regents.

Mr. Mehnert reported on the following actions since that time: A private firm was engaged to help with planning the education/outreach program--especially those aspects of it connected to the NLM Sesquicentennial. Plans are well along to contract with a private firm to work with the Library to carry out many of the planned activities. A calendar was distributed to the Regents listing month by month the activities planned for 1986. Mr. Mehnert reviewed the items briefly and solicited additional suggestions from the Regents. Following his remarks, Mr. Mehnert showed the Board two new videotapes: one about the Toxicology Information Program and the other a remake of the NLM film, "Communicating for Health."

During the following discussion, the Board made it clear that the Library's 150th anniversary should not be the end of the outreach process, but its beginning. Dr. DeBakey emphasized that the calendar was a fluid document and urged the Regents to suggest additional items. She also suggested that in articles about NLM written by Regents and staff they try to incorporate quotations from prominent health professionals about the value of NLM's services. Dr. Abdellah made several specific suggestions about adding more international involvement to the calendar. Dr. Bowles asked that Mr. Mehnert notify the Regents about the availability of the NLM videotape and also slides they might use in making presentations about the Library; he emphasized the importance of using the videotape at exhibits and at professional meetings. Mrs. Echelman suggested making the videotape available to large public library systems that have substantial science collections.

## IX. UPDATE ON THE TIME PROJECT

Dr. William Harless of the Lister Hill Center, Director of the Technological Innovations in Medical Education (TIME) Project, discussed recent changes in the experimental interactive teaching program. "The Case of Frank Hall." This project simulates the interaction between patient and health professional and utilizes three technologies: microcomputer, voice recognition, and videodisc. It was demonstrated to the Board at their meeting in October 1984. Although the goal of the project has not changed--to investigate the state of the art in instructional technology and its application to problems in health education--a number of changes have been made in the Frank Hall program in response to suggestions made by the Regents and others. Among the changes: an interdisciplinary peer review group has been set up for the TIME project; the pace of the program has been increased; the surrogate doctor has been removed--the student is now the doctor and interacts with the patient; the possibility of a crisis has been introduced during the hospitalization of the simulated patient; built-in evaluation of the student's performance has been improved even more; background music has been reduced, and certain inaccuracies in the simulation have been eliminated.



Dr. Harless discussed the unique features of the TIME project: uncued user interaction by voice input; multiple health problems of the simulated patients which require multiple diagnoses for management; a full range of medical, social, and clinical information about the patient available to the student; the realism of the simulated clinical environment is enhanced by randomly generated probability-based occurrence of outcomes; the drama of the simulation is enhanced by a dynamic, time-related management process requiring timely and appropriate intervention by the student. All these capabilities are in the present model and can be demonstrated. In addition, there is a special vocabulary of "educational control words" that may be called on by the student to acquire more information and a deeper understanding of the situation or concept--"sounds," "interpretation," "definition," "thoughts," etc. The model has been presented to the senior staff of the Library and successfully demonstrated at a number of national meetings and for other government agencies. Dr. Harless concluded by noting that two more TIME simulations are under development to (1) determine the validity of the model in evaluating the clinical performance of medical students; (2) establish an efficient process of creating the materials; and (3) document the precise costs for developing these simulations. It is expected that the developmental phase of the project will be completed by the end of FY 1986.

#### X. REPORT OF THE NOMINATING COMMITTEE

Mr. Welsh, chairman of the committee to recommend a Board chairman for 1985-86, placed the name of the current chairman, Dr. Bowles, in nomination. The chairman absented himself, and Mrs. Echelman presided over his unanimous reelection.

#### XI. NLM DIRECTOR'S AWARD

Dr. Lindberg presented the 1985 NLM Director's Award to Karin K. Colton, NLM Committee Management Officer. She was cited for her outstanding performance in the management of NLM's public advisory committees and her efficient planning and arrangements of their meetings. The Board of Regents had enthusiastically endorsed this award, Dr. Lindberg said.

#### XII. SUPERFUND AND TOXICOLOGY INFORMATION PROGRAM

Dr. Henry Kissman, NLM Associate Director for Specialized Information Services, reported about the Library's activities connected to the "Superfund Act." Section 104(i) of the Act requires the "Establishment and Maintenance of an Inventory of Literature, Research, Studies on the Health Effects of Toxic Substances." A newly created agency at the Centers for Disease Control in Atlanta is the lead organization for Superfund activities in HHS. The Library's Toxicology Information Program (TIP) receives funds to carry out related projects under an interagency agreement. NLM is contributing to the effort by enhancing its existing files: CHEMLINE, TOXLINE, RTECS, and the Toxicology Data Bank. Together, these databases are the "inventory" called for in the Act. Dr. Kissman described how the files are being augmented by adding new data. Prompted by the Act, NLM's Toxicology Information Program is also working on improving access to information files, especially in the case of a chemical emergency.

Dr. Kissman described a new retrieval system that will be initiated by NLM on July 1--the Toxicology Data Network (TOXNET). It will be open to all present MEDLARS users as well as to others. Initially, TOXNET will have two online files available 24 hours a day, seven days a week: the Toxicology Data Bank (TDB), and the Hazardous Substances Data Bank (HSDB). Other toxicology and environmental data files will be added to the network later.

The two initial files have been mounted on the Data General computers of an NLM contractor. The two data banks are somewhat overlapping in content, with the HSDB containing more extensive data (140 elements compared to 94 for each of the 4100 substances they contain). The files, which have enhanced search and print features, are built and maintained online by contractors and NLM staff. A menu-driven search capability will be added to TOXNET later this year which will make the files easier to search for the novice or occasional user. An ELHILL version of the Toxicology Data Bank will remain in NLM's MEDLARS online network through the end of this fiscal year.

Dr. Kissman also described progress on developing a microcomputer workstation that could be conveniently used for rapid access to a variety of databases, especially in the event of chemical spills or other accidents. This TIP project is a collaborative one with NLM's Lister Hill Center and with the Centers for Disease Control. The chemical emergency response workstation will initially run on IBM PC/XT and PC/AT machines, but eventually will be able to run on a variety of microcomputers. The workstation, located at regional EPA and CDC headquarters and staffed by trained personnel, will have access to many remote chemical and toxicological databases. It will be connected to smaller portable microcomputers that are now being made available to the emergency response teams for transportation to emergency sites. Dr. Kissman described briefly a related project now in the planning stage: a proposed "expert" system using artificial intelligence for use by those responding to chemical emergencies.

Dr. Kissman summed up by saying that NLM's involvement with the Superfund Act has been a stimulus to the Toxicology Information Program--it has brought additional resources and prompted new and useful activities. Funding levels have been variable, however, and in recent years too low to sustain activities begun earlier. Also, it has recently been difficult for NLM to acquire additional staff to carry out the new projects.

### XIII. REPORT OF THE ASSOCIATE DIRECTOR FOR EXTRAMURAL PROGRAMS

Dr. William G. Cooper stated that the FY 1985 budget for the Extramural Programs remains essentially the same as discussed at the January Board meeting. He briefly touched on the IAIMS initiative and noted that it continues to be of great interest in the community. The proceedings of the October IAIMS Symposium were published recently and have been distributed widely. A copy was included in the agenda folder. Another symposium is planned for March 12, 1986, during the Extramural Programs Week of the NLM Sesquicentennial.

Dr. Cooper then commented on an issue of importance to NIH, specifically to Dr. Wyngaarden, and the research community. During the Director's Advisory Committee meeting last November and at later NIH staff meetings, discussions were held on how NIH's extramural support programs could be improved. The issue is still under discussion and centers around the element of more opportunities for



longer tenure of support mechanisms, allowing the investigator to perform research under more stable conditions. The proposal that is currently under consideration, Dr. Cooper said, is a Method to Extend Research in Time (MERIT) award and would not require preparation of a new application. NIH staff, together with Councils and Boards, would identify outstanding investigators to receive the MERIT award outright. The additional support for an investigator-initiated research award considered under this mechanism would be up to seven years. The list of investigators would be highly selective and would concentrate on those with proven track records. Dr. Bowles expressed his concern regarding the availability of funds for younger investigators if the MERIT award proposal goes into effect. It was Dr. Cooper's opinion that those outstanding younger investigators would not be severely affected. Mrs. Echelman pointed out that it would be at least useful to take into consideration whether the outstanding, experienced investigators would be able to draw on private foundation funds to continue their work, funds not available to young investigators. Dr. Wyngaarden is especially concerned about the young investigators, Dr. Lindberg said, and NIH support of their research will be considered in the decisions that will eventually be made.

---

MEETING CLOSED FOR THE REVIEW OF GRANT APPLICATIONS, 9:20 A.M., JUNE 7, 1985

---

#### XIV. REVIEW OF PENDING APPLICATIONS

Before proceeding with the consideration of pending applications, Dr. Roger W. Dahlen, Chief, Biomedical Information Support Branch, EP, informed Board members of confidentiality and conflict-of-interest procedures and reminded them to sign, at the conclusion of the grant application review, the statement that they had not participated in the discussion of any application where conflicts of interest might occur.

The Board concurred with 66 recommendations of the Extramural Programs Subcommittee which met on June 5. Five applications, on which the Subcommittee had not acted, were deferred by the Board. In summary, the Board reviewed 71 applications of which 32 were recommended for approval, 34 for disapproval, and 5 for deferral. Grant applications recommended for approval by the Board are listed in the summary actions (Attachment B). Interim actions taken by the Extramural Programs staff since the January Board meeting were noted.

During the review of Resource Grant applications, a policy question arose on the continued funding of library automation projects under this program. The Board unanimously passed a motion instructing the Extramural Programs' staff to review the entire Resource Grant Program criteria, specifically with regard to funding of computer hardware, and report back to the Board in September with recommendations for a possible change to the existing policy.

#### XV. ADJOURNMENT

The meeting was adjourned at 11:30 a.m., Friday, June 7, 1985.

\*\*\*\*\*

Wednesday, June 5, 1985, 3:00 to 5:30 p.m.  
(EP Subcommittee--List of Attendees under Attachment C)  
Thursday, June 6, 1985, 9:00 a.m. to 4:30 p.m.  
Friday, June 7, 1985, 9:00 a.m. to 11:30 a.m.

\*\*\*\*\*

#### ACTIONS TAKEN BY THE BOARD OF REGENTS

1. The Board moved to endorse the letter sent by Dr. Lindberg to the Office of Management and Budget (OMB), expressing concern about the OMB circular on Federal information management policy.
2. The Board unanimously passed a motion to accept the general outline of the NLM planning process, with the draft plan to be presented to the Regents at the June 1986 meeting.
3. The Board reelected Dr. Bowles to serve as the Regents' Chairman for another year to August 3, 1986.
4. The Board unanimously passed the motion instructing the Extramural Programs' staff to review the entire Resource Grant Program criteria, specifically with regard to funding of computer hardware, and report back to the Board in September with recommendations for a possible change to the existing policy.
5. The Board concurred with 66 recommendations of the Extramural Programs Subcommittee; it deferred five applications on which the Subcommittee had not acted. Grant applications for approval are listed in the summary actions (Attachment B).

\*\*\*\*\*

I hereby certify that, to the best of my knowledge, the foregoing minutes and attachments are accurate and complete.

*D.A. Lindberg, MD 7/12/85*  
Donald A. B. Lindberg, M.D. (Date)  
Executive Secretary

*L. Thompson Bowles, M.D., Ph.D. 7/12/85*  
L. Thompson Bowles, M.D., Ph.D. (Date)  
Chairman



CHAIRMAN

BOWLES, L. Thompson, M.D., Ph.D. (8/3/86)  
 Dean for Academic Affairs and  
 Professor of Surgery  
 The George Washington University  
 Medical Center  
 2300 I Street, N.W. #713  
 Washington, DC 20037 202-676-3501

DeBAKEY, Lois E., Ph.D. (8/3/86)  
 Professor of Scientific Communications  
 Baylor College of Medicine  
 1200 Moursund Street  
 Houston, TX 77030 713-790-3185

ECHELMAN, Shirley (8/3/85)  
 Director  
 Association of Research Libraries  
 1527 New Hampshire Avenue, N.W.  
 Washington, DC 20036 202-232-2466

FENWICK, Russell L. (8/3/88)  
 Senior Vice President  
 Facilities and Contingency Planning  
 Bank of America  
 Dept. 3629  
 P.O. Box 37000  
 San Francisco, CA 94137 415-622-4935

GUNN, Albert E., M.D. (8/3/87)  
 Associate Dean for Admissions,  
 The University of Texas Medical School  
 at Houston, and  
 Medical Director, Rehabilitation Center  
 University of Texas/M.D. Anderson  
 Hospital and Tumor Institute  
 6723 Bertner Avenue 713-792-3580 a.m.  
 Houston, TX 77030 713-792-4711 p.m.

LOPEZ, John K. (8/3/87)  
 Executive Vice President  
 Medicalectrographic  
 Instrumentation, Inc.  
 924 Borregas Avenue  
 Sunnyvale, CA 95098 408-943-1999  
 Mailing Address:  
 Box 2312, Stanford, CA 94305

MOLINE, David O., D.D.S. (8/3/86)  
 Asst. Professor of Dentistry  
 Dept. of Hospital Dentistry  
 University of Iowa  
 Hospital and Clinics  
 Iowa City, IA 52242 319-356-2743

RODKEY, Grant V., M.D. (8/3/88)  
 Assoc. Clinical Professor of Surgery  
 Harvard Medical School  
 25 Shattuck Street  
 Boston, MA 02115 617-742-4180  
 Mailing Address:  
 Zero Emerson Place  
 Boston, MA 02114

STEAD, Eugene A., Jr., M.D. (8/3/88)  
 Prof. Emeritus of Medicine  
 Duke University, and  
 Distinguished Physician  
 Veterans Administration  
 Duke Hospital - P.O. Box 3910  
 Durham, NC 27710 919-684-6587

EX OFFICIO MEMBERSPrimary

BOORSTIN, Daniel J., Litt.D.  
 Librarian of Congress  
 Library of Congress  
 10 First Street, S.E.  
 Washington, DC 20540 202-287-5205

Alternate

WELSH, William J., LL.D.  
 Deputy Librarian of Congress  
 Library of Congress  
 James Madison Memorial Bldg., Room 608  
 10 First Street, S.E.  
 Washington, DC 20540 202-287-5215

Board of Regents Roster (Continued)

Primary

BRALLIAR, Max B., Lt. Gen., USAF, MC  
Surgeon General  
Department of the Air Force  
Bolling Air Force Base  
Washington, DC 20332-6188  
202-767-4343

DITZLER, John W., M.D.  
Chief Medical Director  
Veterans Administration  
Dept. of Medicine and Surgery  
810 Vermont Avenue, N.W.  
Washington, DC 20420 202-389-2596

KOOP, C. Everett, M.D.  
Surgeon General, PHS, and  
Deputy Assistant Secretary for Health  
200 Independence Avenue, S.W.  
Washington, DC 20201 202-245-6467

MITTEMEYER, Bernhard, Lt. Gen., MC, USA  
The Surgeon General  
Department of the Army  
Washington, DC 20310-2300  
202-697-1295

KINGSBURY, David T., Ph.D.  
Asst. Director for Biological,  
Behavioral, and Social Sciences  
National Science Foundation  
1800 G Street, N.W., Room 506  
Washington, DC 20550 202-357-9854

SEATON, Lewis H., Vice Adm., MC, USN  
Surgeon General  
Office of the Chief of Naval  
Operations (OP-093)  
Department of the Navy  
Washington, DC 20350-2000  
202-697-0587

Alternate

BALL, Thomas P., Jr., Brig. Gen., USAF, MC  
Commander  
Malcolm Grow Medical Center  
Andrews Air Force Base, MD 20331-5300  
301-981-3001

HAHN, James M. (142)  
Director  
Continuing Education Resources Services  
Veterans Administration  
810 Vermont Avenue, N.W., Room 875D  
Washington, DC 20420 202-389-2581

ABDELLAH, Faye G., Ed.D., Sc.D.  
Deputy Surgeon General, and  
Chief Nurse Officer, PHS  
Parklawn Building, Room 18-67  
5600 Fishers Lane  
Rockville, MD 20857 301-443-4000

HASTINGS, James E., Col., MC, USA  
Chief, Graduate Medical Education Branch  
Education and Training Division  
U.S. Army Medical Department (SGPE-EDG)  
Personnel Support Agency  
Washington, DC 20324-2000  
202-693-5455

DYSART, Noel, Capt., MC, USN  
Asst. for Professional Training  
Office of the Chief of Naval  
Operations (OP-939D)  
Department of the Navy  
Washington, DC 20350-2000  
202-653-1752

EXECUTIVE SECRETARY

LINDBERG, Donald A. B., M.D.  
Director  
National Library of Medicine  
Bethesda, MD 20209 301-496-4725

APPLICATIONS APPROVED BY COUNCIL 1/  
(ARRANGED NUMERICALLY BY PROGRAM)

ALLIANCE:11 "B"

INSTITUTE/DIVISION: NATIONAL LIBRARY OF MEDICINE

COUNCIL DATE: MAY 1985

APPLICATION NUMBER	PROJECT TITLE	AMOUNTS RECOMMENDED
1 R01 LM 03120-07	EXPERT COMPUTERIZED BIBLIOGRAPHIC SEARCH ASSISTANT	07 88,630 08 92,975
1 R01 LM 04229-01A1	PSYCHIATRIC ETHICS CASEBOOK: A MODEL FOR CLINICAL ETHICS	01A1 28,176 02 29,585 03 31,064
1 R01 LM 04327-01A1	BIOMEDICAL SCIENTISTS AND PATENTS	01A1 38,880 02 38,900 03 39,760
1 R01 LM 04336-01	EXPERT COMPUTER SYSTEMS WHICH CRITIQUE PHYSICIAN PLANS	01 104,224 02 101,859
1 R01 LM 04340-01	BOOKS IN EPIDEMIOLOGY	01 35,380 02 38,260 03 38,795
1 R01 LM 04382-01	THE NEW EPIDEMIOLOGY: ROBERT KOCH AND CHOLERA	01 12,196 02 13,523
1 R01 LM 04385-01	OCCUPATIONAL HEALTH AND SAFETY POLICIES	01 38,988
1 R01 LM 04393-01	UPDATE OF MONOGRAPH "HEPATOXICITY"	01 18,012
1 R01 LM 04398-01	A SYMPOSIUM AND EDITED VOLUME ON THE HISTORY OF PHYSIOLOGY	01 6,319

1/Approval recommendation are not final but are the basis upon which subsequent BID determinations and negotiations will determine final awards.

APPLICATIONS APPROVED BY COUNCIL 1/  
(ARRANGED NUMERICALLY BY PROGRAM)

INSTITUTE/DIVISION: NATIONAL LIBRARY OF MEDICINE

APPLICATION NUMBER	PROJECT TITLE	AMOUNTS RECOMMENDED
1 R01 LM 04400-01	US AND THIRD WORLD PRESCRIPTION DRUG USE AND PROMOTION	01 29,030 02 29,300
1 R01 LM 04401-01	THE SECOND WOOD INSTITUTE CONFERENCE	01 7,750
1 R01 LM 04406-01	CONCEPTS OF CERTITUDE IN MEDICINE/PHYSIOLOGY, 1100-1600	01 31,120 02 760 03 850
1 R01 LM 04414-01	MEDIEVAL SCIENTIFIC AND MEDICAL VIEWS	01 18,930
1 R01 LM 04420-01	KNOWLEDGE MANAGEMENT FOR CLINICAL TRIAL ADVICE SYSTEMS	01 95,205 02 103,159 03 107,906
1 R01 LM 04431-01	NEURO-IMAGING EXPERT SYSTEM	01 159,047 02 130,842 03 139,009

COUNCIL DATE: MAY 1985

1/Approval recommendations are not final but are the basis upon which subsequent BID determinations and negotiations will determine final awards.



APPLICATIONS APPROVED BY COUNCIL 1/  
(ARRANGED NUMERICALLY BY PROGRAM)

INSTITUTE/DIVISION: NATIONAL LIBRARY OF MEDICINE

COUNCIL DATE: MAY 1985

APPLICATION NUMBER	PROJECT TITLE	AMOUNTS RECOMMENDED
1 G08 LM 04424-01	IAIMS PLANNING	01 111,002 02 118,144
1 G08 LM 04425-01	IAIMS PLANNING	01 95,370
1 R01 LM 04464-01	BONEMECH: A MODEL FOR PORTABLE CITATION DATABASES	01 48,547
1 R01 LM 04478-01	AN IAIMS FOR BIOMEDICAL RESEARCHERS	01 218,096 02 188,680 03 198,112

1/Approval recommendations are not final but are the basis upon which subsequent BID determinations and negotiations will determine final awards.

APPLICATIONS APPROVED BY COUNCIL 1/  
(ARRANGED NUMERICALLY BY PROGRAM)

INSTITUTE/DIVISION: NATIONAL LIBRARY OF MEDICINE

APPLICATION NUMBER	PROJECT TITLE	AMOUNTS RECOMMENDED
1 G07 LM 04379-01	MEDICAL LIBRARY RESOURCE IMPROVEMENT GRANT	01 4,000
1 G07 LM 04380-01	MEDICAL LIBRARY RESOURCE IMPROVEMENT GRANT	01 4,000
1 G07 LM 04389-01	MEDICAL LIBRARY RESOURCE IMPROVEMENT GRANT	01 4,000
1 G07 LM 04409-01	MEDICAL LIBRARY RESOURCE IMPROVEMENT GRANT	01 4,000
1 G07 LM 04416-01	MEDICAL LIBRARY RESOURCE IMPROVEMENT GRANT	01 4,253

COUNCIL DATE: MAY 1985

APPLICATIONS APPROVED BY COUNCIL 1/  
(ARRANGED NUMERICALLY BY PROGRAM)

INSTITUTE/DIVISION: NATIONAL LIBRARY OF MEDICINE

COUNCIL DATE: MAY 1985

APPLICATION NUMBER	PROJECT TITLE	AMOUNTS RECOMMENDED
1 G08 LM 04358-01	INTEGRATED LIBRARY SYSTEM	01 189,415 02 104,470
1 G08 LM 04388-01	HSL/MEDLINE	01 185,644 02 51,755 03 15,396
1 G08 LM 04426-01	AUDIOVISUAL COOPERATIVE FOR EDUCATION	01 74,763 02 71,007 03 44,537

APPLICATIONS APPROVED BY COUNCIL 1/  
(ARRANGED NUMERICALLY BY PROGRAM)

INSTITUTE/DIVISION: NATIONAL LIBRARY OF MEDICINE

APPLICATION NUMBER      PROJECT TITLE

1 R23 LM04428-01  
EIDETIC, A CONSULTANT SYSTEM FOR IMAGE-BASED DIAGNOSIS

COUNCIL DATE: MAY 1985

AMOUNTS  
RECOMMENDED

01	35,275
02	35,835
03	36,390



BOARD OF REGENTSEXTRAMURAL PROGRAMS SUBCOMMITTEE MEETING

June 5, 1985

ATTENDEESSubcommittee Members Present:

Dr. Lois E. DeBakey  
Dr. Albert E. Gunn  
Dr. Grant V. Rodkey

NLM Staff Present:

Dr. William G. Cooper, Associate Director, EP  
Mrs. Ruth Bortz, Grants Management Specialist, EP  
Dr. Jeanne L. Brand, Chief, International Programs Branch, EP  
Mr. Brian R. Campbell, Administrative/Grants Management Officer, EP  
Mr. Peter Clepper, Program Officer, EP  
Mrs. Karin K. Colton, Committee Management Assistant, EP  
Dr. Roger W. Dahlen, Chief, Biomedical Information Support Branch, EP  
Mrs. M. Kathleen Nichols, Grants Management Specialist, EP  
Mr. Richard T. West, Chief, Office of Program Planning and Evaluation, EP  
Mr. Randall Worthington, Program Officer, EP  
Ms. Lisa Tamaroff, Grants Clerk, EP

# "PERSONAL CREATIVITY AND PROFESSIONAL CITIZENSHIP"\*

by

JAMES B. WYNGAARDEN, M.D.\*\*

To return to the scene of one's graduation in the role of commencement speaker seems to fit the definition of what has been called an "insurmountable opportunity." But it is a welcome opportunity--and I am grateful for the invitation.

The title of my talk, "Personal Creativity and Professional Citizenship," is an impressionistic statement that among other things reflects my own interest in the startling increases in knowledge that have taken place during the years since I sat where you are sitting today. In 1948, the year of my graduation, we had penicillin and streptomycin--but no other antibiotics--no (chemical) drugs for treatment of TB, no antidepressants--only a few first generation chemotherapeutic agents for cancer; for example, nitrogen mustard for Hodgkins disease. There were no organ transplantations--almost no vascular prostheses, no vein grafts, no electrical rhythm conversions, no pacemakers. We knew nothing useful about DNA structure. We had no insights into the genetic code.

In the years since I graduated I have been a witness to profound transformations in our knowledge of biology and in our ability to intervene in the treatment of disease. Recently I have been privileged to take an active part in the direction of our national medical research effort. My day-to-day activities at the National Institutes of Health center on research programs--on the health of institutions. But all the while I am fully aware that the indispensable element in all our programs is the spark of individual creativity.

In the fascinating book, "The Eighth Day of Creation," Horace Freeland Judson commented on discovery, creativity, and the nature of the scientific effort. He addressed the subject by asking, "How individual or how social, communal or collective is the making of a great discovery?" In his view, "The fact that scientific routine can be carried out by teams, (and) can even be published by teams says nothing for sure about discovery." Judson argued that "In defense of scientific individualism, it must be said that in the process of discovery, there comes a unique moment; where great confusion reigned, the shape of the answer springs out or at least the form of the question. The insight occurs in the prepared mind of some one person. . . . yet, from the collective viewpoint, it must be said that the insight, however exalting, is not the discovery; it is a moment at the end of a process and the beginning of another." He then described the continuing function of scientists by remarking that "What the insight touches off, even

---

\*Commencement Address at the University of Michigan Medical School, Ann Arbor, Michigan, June 7, 1985.

\*\*Director, National Institutes of Health, Bethesda, Maryland.

before anything gets published, is the familiar and characteristic work of the scientific community; criticism, modification and development of the consequences."<sup>1</sup>

Your obligations as physicians and scientists entail the exercise of both personal creativity and constructive citizenship in the professional and scientific communities. Your individual responsibility to maintain the pace of creative innovation is in no way diminished by the progress that has been made in recent years--in fact, you have an even greater challenge than my classmates and I faced when we graduated.

I do not wish to dwell upon the challenge of the future to such a degree that I downplay the significance of the individual achievements being recognized by exercises such as this. I am aware that it has not been easy for members of the Class of 1985 to reach this point and I extend to you my heartiest congratulations. Each of you has excelled and the degrees being conferred on you are badges of excellence.

Creativity and excellence are closely related, for creativity can be and often is the producer as well as the product of excellence.

The word "excellence" implies competition. If we say that something or someone is excellent, the statement has little meaning unless we can supply the context--"compared with what?" For the individual, we usually make the obvious comparison--that is, competition with others--as our standard of excellence.

We often refer to universities or research institutions as centers of excellence. In doing so, we are describing more than a magnificent facility populated by a community of distinguished scientists and educators. The excellence in such centers is much more likely to be the result of a constant interaction that draws out from students, scientists and faculty alike the extra effort and dedication that would not be demanded in a less competitive setting. This, by the way, is why such great care is exercised in selecting students for admission to medical school. The quality of a school is to a very great extent determined by the quality of the students it accepts.

Lewis Thomas, in looking back on his own experience as a medical student, attributed much of his education to his fellow students. In his book, "The Youngest Science," Dr. Thomas remarked, "When I am asked . . . which member of the Harvard faculty had the greatest influence on my education in medicine, I no longer grope for a name on that distinguished roster. What I remember now from this distance is the influence of my classmates. We taught each other; we may even have set careers for each other without realizing at the time that so fundamental an educational process was even going on."<sup>2</sup> But let me return to excellence, competition, and the Class of 1985.

In 1978, the presidents of 15 leading American universities jointly authored a report called, "Research Universities and the National Interest." In the report, the presidents made a general statement which, without using the word, is a commentary on excellence.



"First-rate work in any field of human action is rare and difficult," they said, "but nowhere is the quality of work more decisive than in higher learning and research. It is hard to tell in advance who will do first-class scholarly and scientific work. Sometimes such work is recognized only slowly. Moreover, when a problem is extraordinarily resistant, even first-class work can fail. But none of these qualifications detracts from the force of the proposition that it is quality that counts." In the simple words of (the late) Philip Handler, "In science, the best is vastly more important than the next best."<sup>3</sup> The same could surely be said of the practice of medicine.

Excellence is an ephemeral term. What is excellent today may tomorrow be mediocre. So the person who would be excellent must be currently informed; that is to say, sustained excellence is utterly dependent upon continued learning.

Sheer talent does not equate to excellence. Keeping fully informed is essential but does not guarantee maintenance of excellence. Unless it is put to risk in performance, excellence soon fades. It is ultimately the quality of performance that counts. It is in the application of excellence that we encounter creativity. Creativity might roughly be defined as "dynamic excellence."

Creativity takes many forms. Wherever it is applied--in the practice of medicine--in research--in teaching--in administration--it carries with it the qualities of excellence, the spirit of inquiry, and the application of curiosity and imagination.

It is not easy to describe the process of creativity. Sir William Osler had his explanation for creative progress in medicine. He said, "A master word . . . is directly responsible for all advances in medicine over the past twenty-five centuries . . . the master word is 'work.'"<sup>4</sup> But in Sir Alexander Fleming's account of the discovery of penicillin, a dramatically different quality of creativity is suggested; namely, the role of chance. He said, "There are thousands of different molds and there are thousands of different bacteria and that chance put that mold in the right spot at the right time was like winning the Irish Sweepstakes."<sup>5</sup>

The great French scientist, Claude Bernard, echoed Fleming's comment about the accidental nature of creativity, but added another important dimension to the thought. Bernard said that "Experimental ideas are very often born by chance as the result of fortuitous observations--we walk, so to speak, in the realm of science and we pursue what happens to present itself accidentally to our eyes."<sup>6</sup> The same idea was economically expressed by Franklin P. Adams, when he said, "I find that a great part of the information I have was acquired by looking up something and finding something else on the way."

Perhaps it is useful to underline the fact that both Bernard and Adams linked creativity to activity. Serendipity is seen as a dividend of action.



Any discussion of the role of chance as it relates to creativity in science is incomplete, however, without the moderating words of Louis Pasteur--"Chance favors only the prepared mind."<sup>8</sup>

The variety and power of preventive and therapeutic measures that we take for granted in 1985 would have seemed miraculous fifty years ago. Recall that sulfanilamide was discovered to have therapeutic value only in 1935. The modern era of medicine is often described as beginning with that event. But medical historians correctly remind us that the useful application of the miracle drugs was possible only because the necessary preparatory work had been done. For example, before penicillin could be identified as a powerful means for preventing rheumatic fever, it was necessary to have perceived the connection between the disease and streptococcal infection. The supremely valuable uses to which the chance discovery of penicillin was put depended in most cases upon preparation through decades of labor in the infectious disease laboratories; once again validating Pasteur's observation about preparation for chance.

There is creativity in the long hard pull of meticulous observation as well as in the flash of insight. There is creativity in the practice of medicine as well as in the conduct of basic research. To assume that new medical insights always begin in the laboratory and are built on fundamental research is to overlook the important instances in which the initiating event was a bedside observation.

Along with the opportunities for creative contributions in medical practice and research, there are opportunities--perhaps I should say obligations for the exercise of professional citizenship. The professional citizenship to which I refer is more than active participation in specialty societies or in the medical organizations that will seek you. It is playing a role in the great events of your time.

A clear suggestion of what I have in mind was expressed by Sir Harold Himsworth. Sir Harold commented that "When future historians look back at the period in which we are now living, they are likely to see it as that time in which scientific knowledge emerged from adolescence to become a major factor in the affairs of human society."<sup>9</sup>

This observation is particularly applicable to medicine. In just over two generations, we have acquired the means for attacking many medical problems formerly considered insoluble. These new found abilities have generated a set of societal issues we have not faced before.

From this time forward, physicians with increasing frequency will encounter variations of a most difficult question. In starkest terms, the issue is this: Can we afford to continue to live by the deeply ingrained national philosophy that everything that can be done for a patient must be done, at public expense if necessary? It is startling to realize that in recent public discussions concerning heart transplants, e.g., the issue was not the odds for success of the operation but whether it should be removed from the list of experimental procedures for purposes of medicare insurance coverage.

News articles on liver transplants are seldom concerned with the remarkable accomplishments in science that made such procedures even thinkable--the news is how funds were raised to pay for the surgery or how a donor was found. Heart and lung transplants, the artificial heart, artificial pancreas, artificial joints--all of these demonstrate what can be done.

Permit me to reminisce briefly. At the time of my graduation from this medical school, the course of renal failure was predictable. All we could do was to prescribe a low-salt, low-protein diet, and treat infection and heart failure. With the onset of a pericardial friction rub, life expectancy was about two weeks. As an emergency measure, dialysis was a primitive, uncertain and time-limited procedure, available in only a few university hospital centers.

By the mid-1950's, the first successful kidney transplants had taken place and, in the succeeding years, improvements in treatment technique had progressed to the point where in the late 1960's the concerns of patients' families and of physicians primarily focused on means to provide funds for the available costly treatment modalities: dialysis or transplantation.

In 1972, the Federal Government ventured into the support of treatment for catastrophic illness with the enactment of the End-Stage Renal Disease Program. This program is a prime example of the American medical philosophy of "what can be done, must be done." The ESRD treatment program is one of the costliest single treatment programs in the history of medicine. Currently, it costs \$2.4 billion dollars per year. Its costs are essentially uncontrollable, and it is highly unlikely that its coverage will be reduced. Now, a decade later, we are facing parallel issues in liver transplantation, heart transplantation, the artificial heart, the artificial pancreas. It is sobering to project from the End-Stage Renal Disease Program experience the potential costs of these programs to the Nation, and to the taxpayer. Should these procedures also be covered by Federal dollars? These are major policy issues on which public opinion will ultimately exercise control. But the public must be accurately informed of the implications of its decision. An important term of this question is--can we as a Nation afford this lengthening list of expensive technologies for all patients who might benefit from them?

Before you attempt an answer, let me propose an alternative. The examples I have used are examples of what Lewis Thomas has called "halfway technologies"--none of them the real answer to the serious conditions to which they are applied. The way out of the economic dilemmas is to make such technologies unnecessary. That is, to search and find the knowledge that will lead to the prevention of end-stage renal or liver or heart disease. The ultimate solution will be reached through medical research and the discovery of strategies for the prevention of disability and premature death. That is the reason that one-fourth of the NIH budget, or more than one billion per year, is directed toward prevention-oriented research.



But meanwhile, you as newly graduated physicians are challenged to the exercise of constructive citizenship in seeking both the economic and scientific answers to the problems of halfway technology.

Such problems are difficult, but there is another set that is even more so. I speak of the need for clearheaded consideration of some of the ethical dilemmas that will be created not only by the economic realities that accompany technological innovation but also by the more profound questions that may arise from our further progress in molecular genetics. This generation of scientists and physicians will be called upon to explain to patients and the general public the great promise offered by somatic cell gene therapy in the treatment of inherited disease and the difference between such intervention and introducing changes in the gene pool.

You as members of the Class of 1985 enter your profession at a very challenging and difficult time. You will need more than ever to focus on the patient, and to guide him or her through the strange and forbidding world of hi-tech medicine. In employing the newer procedures, we need exercise no less of compassion. In fact, many of the new procedures such as CT scanning or nuclear magnetic resonance imaging are compassionate procedures in that they make unnecessary more painful studies and provide definitive diagnoses in shorter time. But this needs explaining--and as doctors you must be sure to take time to listen to your patients and to talk with them.

Whatever your career choice within the realm of medicine, you have a responsibility as an enlightened citizen to deal constructively and compassionately with the economic and ethical issues of your day.

I can think of no better way to summarize than to quote a brief paragraph from an essay by Lewis Thomas on "Medical Lessons From History." He was discussing the possible responses that modern medicine can make to the major disease problems that so far have resisted medical progress.

"The quick and easy way," he said, "is to conclude that these diseases not yet mastered are simply beyond our grasp. The thing to do is settle down with today's versions of science and technology and make sure that our health care system is equipped to do the best it can in an imperfect world. The trouble with this approach is that we cannot afford it. The costs are already too high and they escalate higher each year. Moreover, the measures available are simply not good enough. We cannot go on indefinitely trying to cope with heart disease by open heart surgery carried out at formidable expense after the disease has run its destructive course. Nor can we postpone such issues by oversimplifying the problems, which is what we do . . . by attributing so much of today's chronic and disabling disease to the environment or to wrong ways of living. The plain fact of the matter is that we do not know enough about the facts of the matter and we should be more open about our ignorance."

But I would not wish to leave Lewis Thomas on this downbeat note. He went on to say paradoxically that there has never been a period in medicine when the future looked so bright. He amplified this thought as

follows: "There is within medicine," he said, "somewhere beneath the pessimism and discouragement resulting from the disarray of the health care system and its stupendous cost, an undercurrent of almost outrageous optimism about what may lie ahead for the treatment of human disease if we can only keep learning."<sup>10</sup>

And with that theme, I will close. I salute you, the graduates of the Class of 1985, and wish each of you Godspeed.

X X X X



### References

- <sup>1</sup>Horace Freeland Judson, "The Eighth Day of Creation," Simon and Schuster, New York, 1979, p. 25.
- <sup>2</sup>Lewis Thomas, "The Youngest Science," The Viking Press, New York, 1983, p. 29.
- <sup>3</sup>"Research Universities and the National Interest," Ford Foundation, 1978, p. 5.
- <sup>4</sup>James H. Austin, "Chase, Chance, and Creativity," Columbia University Press, New York, 1978, p. 185.
- <sup>5</sup>Ibid., p. 89.
- <sup>6</sup>Ibid., p. 1.
- <sup>7</sup>Ibid., p. 8.
- <sup>8</sup>Judith P. Swazey and Karen Reeds, "Today's Medicine, Tomorrow's Science," NIH 83-244, U.S. Department of Health and Human Services, Washington, 1983, p. 7.
- <sup>9</sup>James A. Shannon, Editor, "Science and the Evolution of Public Policy," Rockefeller University Press, New York, 1973, p. 31.
- <sup>10</sup>Lewis Thomas, "The Medusa and the Snail, The Viking Press, New York, 1979, pp. 165-166.

## OPENING REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

As part of our preparations for the NIH centennial, some staff members have been digging in files, attics, and other archives for items of historical interest. A few days ago, someone came across a photograph--made in the mid-1930s--showing what appears to be the entire staff of the National Institute of Health standing on the steps of the Headquarters Building at 25th and E Streets. Possibly a good many were absent because obviously it was a winter day but, by head count, 63 professional and support personnel showed up for the picture.

Another photograph was found of the full staff of NIH made some 10 to 12 years later. It was taken on the wooded hillside that later became the site of Building 31. An accurate count of the people in the picture would have been difficult but, according to the NIH Almanac, there were fewer than 2,000 full-time Civil Service and Commissioned Corps personnel assigned here at that time. Since then, our numbers have grown by a factor of six.

As far as I know, there have been no recent attempts to photograph a gathering of all of the people of NIH, although the idea has been suggested as a centennial event. Long ago, we gave up the idea of having a meeting involving more than a minor

---

\*NIH Honor Awards Ceremony, June 17, 1985, Masur Auditorium.

\*\*Director, National Institutes of Health, Bethesda, Maryland.

fraction of our complement of personnel. Masur is our largest auditorium, but we can accommodate here only about 4 percent of our total population.

However, there is something special about the audience at this award ceremony because it is truly representative of our community. There are persons here today from almost every organizational unit as well as from the surprisingly broad range of skilled personnel needed for the successful operation of this unusual agency. Each of us faces a different set of challenges each working day--and we each bring to our assigned tasks an individual set of abilities, training, and experience. But we have a common vocation, a call to excellence, and as different as our activities may be, we can all enjoy the genuine satisfaction that comes from the unreserved investment of our individual talents in jobs worth doing.

In today's ceremony, we give deserved recognition to a relative few from our midst who typify the many. One gets a sense of the scope of NIH by reviewing the range of occupational categories from which our awardees were selected. Although the citations that appear in the programs are necessarily brief and somewhat restrained, they suggest an astonishing array of accomplishments.

In today's ceremonies, it will be my privilege to present the NIH Director's Award, the Outstanding Service Medal and Outstanding Unit Citation for Commissioned Officers, and two special awards for Equal Opportunity Achievement. One of the latter category--the Harvey J. Bullock, Jr., Award for Equal

Opportunity Achievement--is made in recognition of the late Mr. Bullock's efforts and achievements in this area. It is given to recognize significant individual efforts in furthering equal opportunity by persons who are not EEO program leaders.

The NIH Equal Employment Opportunity Award of the Year is given to the person selected NIH-wide from among those who have received cash EEO Special Achievement Awards during the year from within the Bureau, Institute, or Division where they are employed.

The PHS Outstanding Service Medal is presented to officers who have demonstrated outstanding continuous leadership in carrying out the mission of the PHS, or have performed a single accomplishment which has had a major effect on the health of the Nation, or have performed a heroic act resulting in the preservation of health or property.

The PHS Outstanding Unit Citation is made to officers who exhibit superior service toward achieving the goals and objectives of the PHS.

Although the NIH Director's Award is relatively new, it has come to have special meaning. The award is designed to recognize exceptional performance by personnel in the Civil Service as well as in the Commissioned Corps. It is for persons who have made substantial or exceptional contributions to the benefit of the programs or to the people of the NIH. By definition, the awardee's work performance must be clearly outstanding and directly related to fulfilling the NIH mission.

The choices among the many nominees for these awards are never easy ones. In evaluating the nominations, careful attention



was given to such points as the extent to which the field of health or biomedical research has been strengthened or improved by the individual's particular superior service or achievement. Another criterion is the extent to which the applied ideas, concepts, and so forth represent originality, creativity, or initiative. A point of special interest is the extent to which competence or resourcefulness improve the scientific or administrative management of the NIH. Some will receive the Director's Award in recognition of a high degree of demonstrated skill and leadership in administration or in science.

I feel sure that as you hear the citations read, you will share my feeling of pride in being associated with the people of the NIH.)

## INTRODUCTORY REMARKS

- o The subject of today's meeting, biotechnology, is a topic of intense discussion in settings ranging from the halls of academe to the boardrooms of major corporations. And every week articles on biotechnology appear in publications as diverse as Science magazine and the Wall Street Journal.
- o The NIH has a special interest in the future of biotechnology since this fledgling industry owes its existence, in large measure, to the sustained support provided by the NIH over the past several decades to basic research in molecular biology.

### Biotechnology Defined

- o Biotechnology has been defined broadly as any technique that uses living organisms (or parts of organisms) to make or modify products, or to improve plants or animals for beneficial use. Included under this broad definition would be the type of industrial fermentation that has been used for centuries in making bread, cheese, and alcoholic beverages along with the practice of selective breeding that has been employed to enhance the properties and characteristics of plants and animals for human use. However, there has emerged, largely within the last decade, a "new" biotechnology which has its roots in the science of molecular biology and is comprised of a collection of powerful techniques that can be applied to

develop products of commercial value. Most notable among these new tools are (1) recombinant DNA technology (the so called gene splicing technique) which permits direct manipulation of the genetic material of individual cells to control the production of biological materials, (2) cell fusion in which different types of cells are artificially joined to combine the desirable characteristics of each into one cell, and (3) bioprocess technology which allows the adaptation of biological methods of production to large-scale industrial use.

oo It is essentially this "new" biotechnology to which we will be addressing our discussions today.

oo We will hear much more about the evolution and uses of these techniques in later sections of this meeting.

#### The Promise of Biotechnology

o While few products of the incipient biotechnology industry have reached the marketplace to date, it is estimated that future sales of biotechnology products will reach somewhere between \$20 billion and \$100 billion by the year 2000. Most observers agree that the benefits of this new technology will be substantial. For instance,

oo In the area of health care

-- genetic engineering will make possible the production of therapeutically useful amounts of such regulatory proteins as

insulin, interferons, interleukins, growth hormone, tissue plasminogen activating factor, and blood factor VIII;

ooo In fact, clinical trials are being conducted now to test the growth factor for the immune T-cells for treatment of some immune disorders, the tissue plasminogen activator for early treatment of heart attacks, and tumor necrosis factor for treatment of cancer.

- these new techniques will permit the vast improvement of current vaccines and the development of entirely new ones; and
- these new tools also offer promise of providing gene therapy for the treatment of certain diseases.

oo In animal and plant agriculture

- genetic manipulation should lead to increased growth and greater yields, improved feed efficiency, improved quality of plant crops and animal herds, and reduced costs of production; and
- the application of existing techniques holds promise of new veterinary vaccines, diagnostics, and therapeutic drugs.



oo In pollution control

-- microorganisms can be developed to metabolize organic molecules and, thus, detoxify a range of toxic chemicals.

- o These examples are but a few of the potential payoffs that can be perceived now as a result of the current technology, and the continued development of the science base underlying biotechnology along with the additional application of this new knowledge could lead to more important products that cannot now be foreseen.

#### Issues and Concerns

- o As is true of many major advances, the emergence of the biotechnology industry has also created a new set of issues, concerns and challenges.
  - oo Biotechnology was born in an atmosphere of intense public scrutiny and now as the first products of this new industry are beginning to move from the laboratory to the marketplace (and as new uses of the technology are perceived), biotechnology is again the subject of heightened public interest--and in some quarters, heightened concern.
  - oo The earliest concern has been for the safety of laboratory experimentation and the physical containment of altered organisms to assure the protection of the public health and the environment.

- oo More recently concern has centered on the potential effects from deliberate release of genetically engineered organisms.
- oo Increasing debate is also occurring on the safety and ethical considerations of gene therapy for humans, the ethics of using genetic engineering to enhance human capabilities, and the threat of potential uses of biotechnology to develop biological weapons.
- oo In addition to the questions of public safety, environmental health, and ethics surrounding the use of the products of biotechnology, the growing commercial importance of molecular biology has raised questions for universities regarding the effects of the new relationships with industry which this technology has engendered.
- The emergence of a host of cooperative ventures between industry and university scientists is prompting universities to examine the adequacy of their existing policies concerning such matters as faculty conflict of interest, freedom of scientific communication, patenting and licensing of inventions, and protection of the interests of graduate students. In short, universities are acting to assure that traditional academic values are not eroded as a result of commercial interests.
- oo Many of the concerns attendant to the growth and uses of biotechnology are being examined in a variety of forums, and this free-ranging discussion and public debate is serving to place these issues in perspective. Most observers agree that open and frank discussion of

this early stage in the industry's development is both in the public interest and to the ultimate benefit of this new industry.

### Challenges and Goals

- o An entirely different set of issues and challenges grows out of the national need to develop policies and programs to foster the growth of this new industry in a manner that aggressively promotes the position of U.S. biotechnology firms in an increasingly competitive international marketplace.
- oo Three factors are generally concluded to be of overriding importance in determining a country's competitive position in world markets: (1) government funding of basic and applied research, (2) adequate numbers of trained personnel, and (3) the availability of funds for commercial development.
- oo Currently the U.S. appears to enjoy a competitive advantage in each of these areas:
  - There seems to be ample evidence, for instance, that the entrepreneurial spirit is alive and well in this country and that biotechnology firms have been quite successful in attracting venture capital.

-- The United States, as a result of its vast network of university scientists and research institutions, is widely acknowledged as the world leader in both the development of new fundamental knowledge in the areas of molecular biology underlying biotechnology and the training of basic researchers for careers in biomedical investigation.

o However, we must guard against complacency by examining our current efforts in order to determine whether the total research needs of biotechnology are being met, whether the future demands for specific types of specialized personnel are being addressed adequately, and whether the general climate for innovation will continue to be conducive to progress in biotechnology.

oo In FY 1984, for instance, it is estimated that the NIH provided approximately \$408 million of extramural support for research directly related to biotechnology and almost \$967 million for support of the broader science base underlying this field.

-- It has been suggested, however, that a critical need may exist for increased emphasis on generic research of the type that falls between the basic research generally supported by the NIH and the type of proprietary activities undertaken by industry in the development of specific products.

ooo I believe this is an area that may warrant further examination.



oo In FY 1984 the NIH also provided approximately \$29 million for training in areas directly related to biotechnology and about \$49 million for training in the broader science base.

-- A special need may exist, however, for increased training of personnel in certain selected areas of special importance to biotechnology.

ooo In that regard, for instance, the NIH has recently participated with the NSF in funding a new center grant award in biotechnology at MIT to support the training of individuals who will combine engineering and biology in addressing problems in the area of bioprocessing.

oo Currently, the NIH intramural program constitutes a rich resource for research and training in biotechnology.

-- To increase opportunities for cooperative research, to provide additional research training in biotechnology, and to expand access to governmental laboratory facilities and resources, the NIH has developed a proposal for a Research Associateship Program in Biotechnology.

ooo The program is intended to provide postdoctoral scientists opportunities for research on problems which are compatible with the interests of their sponsoring laboratories and contribute to the overall objectives of the NIH intramural program as they relate to biotechnology.

Today's Meeting

- o Many of the issues, concerns, and identified needs in biotechnology are, quite obviously, outside the purview and sphere of influence of the NIH. I mention them today merely to convey a sense of the current context in which we are operating and to set the stage for today's discussion of the appropriate role of the NIH in contributing to the nation's leadership in biotechnology.
- o Before we begin our discussion of biotechnology, Dr. Raub will report on activities undertaken and planned as a followup to our last DAC meeting on strategies to improve the efficiency and effectiveness of the NIH extramural awards system.
- o Then I will preface today's discussion by examining briefly the NIH mission and the principles which, historically, have guided our activities. I will attempt also to describe some examples of special circumstances in which the traditional mission has been extended to meet pressing national needs.
- o Against that backdrop, we will proceed to a discussion of (1) the history and development of new biotechnologies and their future prospects; (2) the elements of a science policy for biotechnology; (3) the role of NIH in the support of training for biotechnology; (4) issues in the risk assessment and risk management of biotechnology; (5) the manpower, financial, regulatory, and information barriers to industrial competitiveness; and (6) the role of NIH in fostering biotechnology.

## HISTORY OF NIH MISSION AND SPECIAL CIRCUMSTANCES SUGGESTING REEXAMINATION

### The Early Years

- o Many of the events and forces that shaped the mission of the NIH occurred in the period beginning near, and shortly after, the end of World War II.
  - oo Efforts during those early years to mount an attack on health problems were aided greatly by enactment in 1944 of Section 301 of the Public Health Service Act which provided a broad authority to conduct research.
  - oo In recognition of the gross inadequacy of the existing base of biomedical knowledge and the woeful lack of scientific manpower and other resources necessary for the conduct of research, the NIH chose to interpret this authority in its broadest sense in developing a long-range strategy to create a strong base of science which would later permit a more direct assault on specific health problems. As part of this strategy the NIH concluded that:
    - the pursuit of basic knowledge would be pursued largely through the support of biomedical research conducted by scientists at universities, and that the capacity of those university departments

(primarily in medical schools) would be strengthened wherever possible;

-- training would be provided to assure a cadre of investigators capable of conducting biomedical research; and

-- the principal source of research support would be the investigator-initiated research project grant awarded on the basis of scientific merit as judged through national competition.

oo Those decisions proved to be especially farsighted and, in the intervening decades, have resulted in the development of a vast network of scientists and research institutions which comprise a biomedical research enterprise of widely acknowledged preeminence. Those early principles have also shown themselves to be enduring, and they remain as basic elements in the current NIH efforts to expand our current base of knowledge.

#### Heightened Expectations

o By the 1960's, continuing reports of progress in biomedical research contributed to increasing public expectations for substantial improvements in the quality of available medical care, and congressional concern was expressed regarding the pace with which new knowledge was being translated into general medical practice.



oo This concern was reflected in the enactment of a broad range of new health legislation designed to improve the quality and availability of health care in the Nation.

-- Included in this legislation was a law in 1965 which established the Regional Medical Program to be administered by the NIH to "assist the Nation's health resources in making available the best possible patient care for heart disease, cancer, stroke, and related diseases" by using regional medical centers as a focus of technology diffusion and information dissemination.

o While the promise represented by the Regional Medical Program was not fully realized, the sentiment behind its creation continued to persist, as demonstrated by the enactment of:

oo the National Cancer Act of 1971;

oo the National Heart, Blood Vessel, Lung, and Blood Act of 1972;

oo the National Diabetes Mellitus Research and Education Act of 1974; and

oo the National Arthritis Act of 1974.

o In effect, this legislation provided discrete program recognition and specific expanded responsibilities for the application of existing knowledge through control and demonstration programs and public education.

### Expanding National Goals and Priorities

- o An expanding set of national goals and priorities has led the NIH to reexamine its mission and functions, periodically, to determine whether opportunities exist to lend its particular strengths and expertise to these emerging needs.
- o During the 1970's, for instance, a strong sentiment continued to be expressed for an increased Federal role in improving the quality of health care through the accelerated application of research results.

### Office of Medical Applications of Research (OMAR)

- o In response to this growing concern, the NIH, in 1977, undertook a searching examination of its existing technology transfer activities with the aim of identifying ways in which these efforts could be strengthened and the capabilities of the agency better focused to increase its contribution to this national objective.
- o The results of this assessment indicated the need to (1) develop formal procedures to enlist the services of the scientific community in the identification and validation of new knowledge having potential clinical application, and (2) provide a permanent organizational structure to coordinate the activities of the components of the NIH and serve as the nexus for interaction with other agencies and outside organizations.

- o As a result of this appraisal, there was established within the NIH the Office of Medical Applications of Research (OMAR) to serve as the focal point for technology assessment and transfer activities at the NIH.
- oo A key element in this process is "consensus development," in which OMAR (in collaboration with the NIH institutes) brings together biomedical research scientists, practicing physicians, consumers, and others in an open forum in an effort to reach general agreement on whether a given medical device, drug, or procedure has potential medical value.
- This information is provided to physicians and to the general public through reports containing conclusions and recommendations about a given technology written by expert and lay members of Consensus Development Conference Panels.
- oo OMAR also coordinates NIH medical and scientific reviews of issues related to Medicare reimbursement for a variety of medical technologies and submits these expert opinions to the Health Care Financing Administration to assist them in their decisions on questions ranging from the appropriateness of continued coverage of existing treatments to the safety and efficacy of new technologies.
- oo In addition, OMAR administers the NIH patent program which promotes the transfer and commercialization of NIH-funded inventions.

National Toxicology Program (NTP)

- o During the late 1970's, yet another growing national concern prompted the NIH to extend its traditional role.
- o For several decades, concern had been growing over the increasing numbers of new chemicals being introduced into the environment and the threat of human disease posed by exposure to these compounds.
- o As information was developed during the 1960's and early 1970's to indicate that many environmental chemical agents interfere with cell replication and, therefore, might have an adverse affect on genetic inheritance, increased resources were devoted to developing fast and inexpensive tests to assess the toxicity of these compounds.
- o Throughout this period, legislation was developed to strengthen the authority of regulatory agencies to control exposure to hazardous substances. This new legislation (including the Toxic Substances Control Act) greatly increased the need of regulatory agencies to know more about the toxicity of environmental agents.
- o Various Federal agencies began to develop or intensify testing programs, many of which were limited in scope and contributed to the appearance of overlap and duplication among programs.
  - oo It became readily apparent that the Nation's testing capacity would benefit from better coordination and program integration.



- o It was against this backdrop that the National Toxicology Program (NTP) was established in 1978 for the purpose of coordinating and strengthening the Department's activities related to the testing of chemicals of public health concern by: (1) expanding and broadening the spectrum of toxicologic information obtained on chemicals selected for testing; (2) increasing the numbers of chemicals tested within available funding limits; (3) developing, coordinating, and validating a series of tests and protocols appropriate for regulatory needs, and (4) communicating results of testing and future plans to governmental agencies, the medical and scientific communities, and the public.
- o The NTP, under the leadership of Dave Rall, the Director, NIEHS, consists of the relevant toxicology activities of the FDA's National Center for Toxicological Research and the CDC's National Institute for Occupational Safety and Health in addition to the programs of the NIEHS.
- oo An Executive Committee, composed of heads of the research and regulatory agencies, serves as the NTP's major advisory group, and a Board of Scientific Counselors reviews the Program for scientific adequacy.
- oo An Annual Plan serves as an instrument for (1) describing the coordination of toxicology research, test development, and chemical testing, (2) presenting current testing strategies, and (3) detailing the accomplishments of the program.

- o The NTP, which was granted permanent status by the Secretary, DHHS, in 1981, has evolved into a major Federal resource for testing of chemicals and represents a leading effort in the world aimed at developing better, faster, and less expensive methods for determining which chemicals may be hazardous.

#### Relevance to Today's Discussion

- o I mention these examples today to underscore the fact that while the generic mission of the NIH remains much the same, the NIH has demonstrated that it does possess the flexibility to extend its mission boundaries in selected areas to meet special needs while guarding against serious distortions of its basic mission or jeopardizing the integrity of its traditional programs.
- o It is on this positive note that I would like to move to our next item on the agenda--the historical development and future prospects of biotechnology.

## FEDERAL SCIENCE POLICY FOR BIOTECHNOLOGY

- o Our current examination of the NIH role in fostering biotechnology is, in effect, a response to part of a larger need which exists to develop a science policy for biotechnology which provides a framework within which the principal elements contributing to a strong biotechnology enterprise can be coordinated and aligned to assure a coherent national effort.
- o That need for a national policy for biotechnology is, in turn, being addressed in a general climate in which some very fundamental questions are being raised concerning the basic purposes of Federal funding for scientific research.
  - oo One expression of this current concern is found in the recent initiation of a comprehensive study of U.S. science policy to be conducted over the next two years by the House Committee on Science and Technology under the chairmanship of Congressman Don Fuqua.
- The study will address such questions as: What are the nation's goals in providing support for science? How do our goals for science relate to our other national goals? Are our goals internally consistent? To what extent do the policies for government support of science which have evolved over the last 40 years (since the report of Vannevar Bush) apply to the next 40 years, and to what extent must changes in policy be made to achieve new and emerging national goals and objectives?

oo Another expression of concern over perceived inadequacies in our current science policies is reflected in the recent Report of the President's Commission on Industrial Competitiveness which underscored a heightened interest in developing a better over-all climate for innovation in this country to combat what has been viewed as a decline in the ability of U.S. industry to compete in world markets.

-- One recommendation of the Commission, in fact, calls for the creation of a cabinet level Department of Science and Technology which would integrate the science components of existing agencies in an effort to strengthen the role of science and technology in contributing to industrial innovation and enhanced competitiveness.

o The Administration, recognizing its responsibility to address the concerns surrounding the development of biotechnology, formed an interagency working group under the White House Cabinet Council on Natural Resources and the Environment to insure that the regulatory process adequately considers health and environmental safety consequences of the products and processes of the new biotechnology.

oo The working group proceeded from the assumption that the manner in which regulations for biotechnology are implemented in the United States will have a direct impact on the competitiveness of U.S. firms in world markets and has attempted to develop a coherent and sensible regulatory process which is based on the best available scientific facts.



oo The working group has developed a "Proposal for a Coordinated Framework for Regulation of Biotechnology" which provides a concise index of U.S. laws related to biotechnology, clarifies the policies of the major regulatory agencies that will be involved in reviewing research and products of biotechnology, describes a scientific advisory mechanism for assessment of biotechnology issues, and explains how the activities of the Federal agencies in biotechnology will be coordinated.

-- The proposal was published in the Federal Register to seek the advice of individuals, public interest groups, industry, and academia on all aspects of the proposal.

- o In addition, in August 1984, the Assistant Secretary for Health established a PHS Ad Hoc Committee on Biotechnology comprised of representatives of each of the PHS agencies and chaired by Frank Young, the FDA Commissioner. The Committee is charged with the responsibility to review the various issues that arise concerning technology and to define differences among the PHS agencies and, where possible, to resolve those differences.
- o It is against this backdrop that we begin today's examination of the elements and strategy of a Federal science policy for biotechnology.

## NIH'S ROLE IN FOSTERING BIOTECHNOLOGY

- o The growth and development of the U.S. biotechnology industry will, undoubtedly, be conditioned by a variety of factors--many of which will have far-reaching implications for industrial innovation, in general, and some of which will have special relevance to the biotechnology industry, in particular.
  - oo As noted previously, many of these factors are beyond the influence of the NIH but they should be recognized and acknowledged as part of the environment in which we must operate since they can exert a strong influence on the ultimate effectiveness of our efforts.
  - oo It is incumbent upon us, however, to sort among the myriad of emerging needs and priorities and to identify that set of activities which represents a logical and natural extension of the current NIH capabilities in an effort to develop appropriate programs to enhance our contribution to the development of a strong U.S. biotechnology industry.
- o As mentioned earlier,
  - oo The NIH, in FY 1984, provided approximately \$408 million of extramural support for research directly related to biotechnology and almost \$967 million for support of the broader science base underlying this field.

oo In FY 1984 the NIH also provided approximately \$29 million for training in areas directly related to biotechnology and about \$49 million for training in the broader science base.

-- And the NIH has recently participated with the NSF in funding a new center grant award in biotechnology to support the training of individuals in areas of bioprocessing.

oo In addition, the NIH intramural laboratories serve as a unique resource for both research and training in biotechnology, and efforts have been initiated to increase opportunities for research training and cooperative research in biotechnology.

o From this examination of our current efforts I would like to address the question of future needs. For instance,

oo What should be the role of NIH in the support of generic research of direct relevance to biotechnology?

oo Are there special training needs that can be addressed by the NIH?

oo What other activities might appropriately be undertaken by the NIH to further the goal of promoting biotechnology.

o I believe our discussion over the last 2 days has served well in setting the stage for this afternoon's discussion of the NIH role in fostering biotechnology, and on that note I would like to proceed.

## AFTER-DINNER ADDRESS\*

by

James B. Wyngaarden, M.D.\*\*

I am delighted to be here with you this second evening of the conference on "The Health Effects of Polyunsaturated Fatty Acids in Seafoods." We have just finished a most delicious and nutritious dinner of salmon. It is reassuring to know that all of the conferees do indeed "practice what they preach."

As the Director of the National Institutes of Health (NIH), I am pleased by the cooperative spirit that exists between the Department of Commerce (DOC), which is responsible for fish and fishery products, and the Department of Health and Human Services (DHHS) as represented by the NIH Nutrition Coordinating Committee (NCC). The coordination of nutrition research between the NIH and DOC has been ongoing since the establishment in 1978 of the Joint Subcommittee on Human Nutrition Research, in the Office of Science and Technology Policy, Executive Office of the President. It is the excellent working relationship between Dr. Artemis Simopoulos, and Dr. John Emerson and Mr. Thomas Billy of the Department of Commerce that led to this conference which is being cosponsored by the NIH Nutrition Coordinating Committee; the National Marine Fisheries Service, National Oceanic and Atmospheric Administration, Department of Commerce; and the National Fisheries Institute.

The objective of the conference, which is to develop a research agenda to determine the spectrum of the health effects of polyunsaturated fatty acids of seafood origin in the American diet, is of particular research interest to the

---

\* Before the Conference on the Health Effects of Polyunsaturated Fatty Acids in Seafoods, Washington, D.C., on June 25, 1985.

\*\* Director, National Institutes of Health, Bethesda, Maryland.



NIH. The National Heart, Lung and Blood Institute, the National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases, the National Institute of General Medical Sciences, and the Division of Research Resources (DRR) have supported research in this area in terms of the effects of polyunsaturated fatty acids on coronary heart disease and atherosclerosis, coagulation, immunology, and inflammation.

In looking for some other relationships between NIH and the Marine Fisheries Service, one item of historical interest that I would like to bring to your attention is that we at the NIH trace our origin to the Hygienic Laboratory set up in 1887 at the Marine Hospital on Staten Island. This Hygienic Laboratory, the NIH precursor, was established for the study of cholera, yellow fever, and other infectious diseases among immigrants and merchant seamen rather than the study of fish oils per se. We plan to make amends.

Recently, as many of you may have noticed, the role of fish in the diet in preventing heart disease, arthritis, and even breast cancer (according to the July issue of Vogue magazine) has received a great deal of attention from the print and television media. The Washington Post, New York Times, and USA Today featured articles on this topic as a result of the publication of three relevant papers and an editorial in the May 9th issue of the New England Journal of Medicine.

I am very much aware of the fact that interest in the health effects of fish oils followed the publication of papers by Bang and Du-Bear on "Plasma Lipids and Lipoproteins in Greenlandic West Coast Eskimos." I am pleased to see that Dr. Dyerberg is a participant at the conference, since these initial observations have led to an outburst of research in this area not only in the United States, but also in Canada, West Germany, England, Australia, Japan, and many other countries.

I commend all of you for your participation in this important conference, and I regret not being able to attend the sessions on current research on the various effects of omega-3 fatty acids on eicosanoid formation, atherosclerosis, immunology and inflammatory response, and membrane function and metabolism. However, I look forward to seeing the conference summary, conclusions, and recommendations for continued research. We hope that the recommendations you make tomorrow may lead to the publication by the various Institutes of Program Announcements that identify their particular research interest.

At this time, I would also like to recommend that we exercise caution in the interpretation of the data, and show some restraint in our enthusiasm about the health effects of polyunsaturated fatty acids in seafoods.

Everything about nutrition is consumed with passion by the public and by all of us. Witness the plethora of statements made about diet and health in terms of preventing heart disease, cancer, arthritis, hyperactivity, learning defects, etc. Let's remember that just a few years ago, the role of chemicals in the environment in producing cancer was greatly overstated by the scientific community, and led to unwarranted fear and concern on the part of the public. Most of the claims of the magnitude of the contributions of industrial toxins have now been retracted, with some damage to the credibility of science, particularly in the area of environmental factors and cancer.

Accordingly, I would urge each of you to evaluate the research data presented at this conference with care, and as further research leads to dietary recommendations, to base your recommendations on solid scientific data that will stand the test of time.

I understand that many of you will further discuss the issue of the health effects of fish oil at the Year of the Ocean Symposium, scheduled for June 27th and 28th at Kingsborough Community College in Brooklyn, New York. I am very

glad to see the active role being taken by the organizers of this conference and NIH-supported investigators in advancing our basic knowledge and understanding in this area, and hope that such advances as those expressed at this conference as well as the symposium will continue in the future.

The rate of progress in the ceaseless war on disease is a function of scientific opportunity, which we now have in abundance, the imaginative insight of scientists such as all of you, and available funds. We are simultaneously involved in the adventure of discovery for its own sake and in pursuit of better health for all. However, we appear to have entered a period of financial constraint in biomedical science. The period of explosive growth of support for biomedical research of the fifties and sixties, when the NIH budget increased at an average rate of 24 percent per year in purchasing power, is long over. The second stage rocket of the cancer, heart disease, and other such initiatives has now played out. The average rate of real growth in the NIH budget from 1970 through 1984 was about 2 percent per year. In my view, we are facing more than a temporary funding constraint in biomedical science; rather we have entered a relatively steady state that all of us, NIH and universities alike, would do well to view as the future norm. Since it may not be possible to continue all of the efforts and programs we have considered meritorious and worthwhile, we will have to set our research priorities carefully, taking into consideration a wide variety of factors; the overall mission of NIH to support research in pursuit of health, scientific considerations, and specific public mandates and assignments as expressed by Congress and the Administration.

At this time any discussion of our FY 1986 budget would have to be mostly speculation. Neither the House Appropriations Committee, nor the Senate Appropriations Committee, has acted upon the NIH budget proposals for 1986. To



add to the uncertainty we do not yet have a final decision on how many new and competing renewal project and center grants we will be permitted to make out of the total \$5.14 billion NIH budget for 1985.

In developing next year's budget the Administration's policy essentially was to freeze domestic programs at the 1985 level. To accomplish this purpose without upsetting the stability of our major research programs the OMB directed adjustments in 1985 spending with regard to the funding of grants. The Congress has questioned those adjustments and as a result we do not now know if we will be permitted to make 5,000, 6,000, 6,500, or some other number of new and competing renewal project grants this year. Similar uncertainty exists with regard to centers grants.

There are encouraging signs, however, that compromises are possible that would resolve our 1985 dilemmas and relieve some of our concerns about 1986. For example, Senator Weicker and OMB have reached agreement on 6,000 new and competing awards for NIH in 1985 and 1986. But this agreement is a component of a larger budget package that has not yet been enacted.

Whatever our priorities and programs, which may vary as conditions and opportunities warrant, there are certain abiding principles that will continue to guide our decisions. One is that the pursuit of basic knowledge is the foundation of all progress in the health sciences. We must continue to increase our store of fundamental knowledge. Any relaxation of that necessarily long-term objective in favor of short-term advantage is a threat to the eventual triumph over disease and suffering.

A second fundamental principle is that investigator-initiated research into biological processes holds the greatest promise of significant discovery. Through competing research projects, we tap the best minds and most creative ideas, weigh them through peer review of substance and methodology, and test



them through challenge and open exchange of information. We will continue to place top priority on the award of new and competing research project grants and on the support of such projects for the life of the award period.

Finally, the third element of these principles is that there is a continuing need to assure a supply of well-trained scientists to carry out the research to meet national health goals.

Human nutrition research, research manpower development, research training, education and information programs are supported by several Federal departments and independent agencies. I am proud that within the Federal Government, the DHHS has the largest human nutrition research program, with the NIH providing approximately 93 percent of the financial support. Nutrition is an important, crosscutting program area within the NIH as it is supported by all 11 Institutes and DRR. For this reason, the nutrition program is coordinated through the NIH Nutrition Coordinating Committee. In FY 1984, expenditures for the NIH program in biomedical and behavioral nutrition research and research training totaled \$192,918,000.

Over the past decade Congress, as well as the public, has shown an increased interest in human nutrition and this interest is reflected in nutrition specific legislation and congressionally mandated interdepartmental coordination. It is the spirit of cooperation that has developed among the various Federal agencies and departments, professional societies, and industry, as well as the mutual support of conferences such as this, which is essential for the continuation of scientific advancements in nutrition research and all areas of biomedical research.

I would like to relate one more piece of history that deals with lipid metabolism. In 1954, Pete Ahrens and associates published a paper on the "Effect on Human Serum Lipids of Substituting Plant for Animal Fat in the

Diet." Thirty years later, Connor and Harris, well-known investigators of lipid metabolism, published "The Comparative Reductions of the Plasma Lipids and Lipoproteins by Dietary Polyunsaturated Fat: Salmon Oil versus Vegetable Oils." I would like to recommend that as research progresses in the area of the health effects of fish oils that investigators make every effort to study the overall diet in terms of its components. As a result of this effort, instead of emphasizing those foods one should avoid, we might be able to recommend in a positive rather than a negative way those foods one should eat to help maintain health and prevent disease based on one's special needs and requirements.

And, the population's interest in fish is certainly evident. In mid-June, The Washington Post's section on new stamps featured the "Creatures of Summer" which included exotic birds on the stamps of New Zealand, Netherland Antilles and Belize; flowers such as orchids on the stamps of Sweden, Belgium and Western Samoa; and rare and unusual fish such as the tasseled anglerfish, pineapple fish, elephant snout fish, lungfish, damsel fish and clownfish on the new stamps of Australia, Uganda, and Palau, a U.S. territory in the Pacific. It is apparent that the current interest in fish is indeed worldwide and crosses many disciplines, one of which is biomedical research.

In conclusion let me cite a Chinese proverb --

If you wish to be happy for one hour, get drunk.

If you wish to be happy for 3 days, get married.

If you wish to be happy for 8 days, kill a pig and eat it.

If you wish to be happy all your life, go fishing (or we could now say, eat fish).

Again, I would like to thank you for the opportunity to be here with you this evening.



174

WELCOMING REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

I am pleased to welcome you to the Clinical Center and the National Institutes of Health.

It seems especially appropriate that we are meeting here in the amphitheater of this handsome Ambulatory Care Research Facility. Less than four years ago, the new facility and the original building were rechristened the Warren Grant Magnuson Clinical Center. The opening of this remarkable building and modernization of the old symbolize the commitment, the challenge, and the continuity of medical research. The additional clinical and laboratory space and expanded capacity for patient care give us an opportunity to explore a wholly new area involving ambulatory care research.

While the hospital and laboratories provide the means for research, the professionals who work here are the lifeblood of the institution. And you, as Medical Staff Fellows, are a necessary and integral part of our research community. You are a select group--youthful, energetic, enthusiastic, creative, and talented--and we welcome you.

---

\*Presented at the Orientation of Medical Staff Fellows, July 8, 1985, ACRF Amphitheater

\*\*Director, National Institutes of Health, Bethesda, Maryland



You will soon be taking on the major responsibilities of patient care. As primary physicians you will be responsible for treatment, for managing complications should they arise, and for carrying out the protocols under direction of an established investigator.

Here at the Clinical Center you will very likely be much more heavily involved in biomedical research. As you know, it is a rigorous and demanding pursuit that requires discipline and hard work, but it offers excitement and intellectual challenge. This campus and this hospital will be your laboratory and work place.

Many of you will devote your time to research in the biomedical sciences, learning research methods and design, and engaging in the logical pursuit of a scientific problem and the critical interpretation of results. Some of you will be participating as dental staff fellows treating patients in the Dental Clinic.

In the laboratory, new and powerful techniques have opened doors at practically every level of medical research. A particular wave of excitement attaches to recombinant DNA technology, to research on oncogenes, their identification, the search for gene products, and the relation to known growth factors. This new method has also opened up unanticipated opportunities to improve old vaccines and develop new ones, and to manufacture biologically active substances, such as hormones, two of which--human growth hormone and insulin--are ready for clinical testing.

The powerful tool of hybridoma technology is already widely used in science and medicine but its full potential is as yet

hardly comprehended. The exquisitely specific monoclonal antibodies should facilitate the development of vaccines, improve diagnostic tests, enhance the immunotherapy of infectious diseases, and provide powerful tools for the diagnosis and treatment of cancer and other diseases. Cell fusion has opened up enormous possibilities in basic and clinical research.

Clinical investigation is a vital segment in the progression from basic research to prevention and treatment of disease, and is of fundamental importance to NIH. The Clinical Center is the largest research hospital in the world. There is much to be done in clinical research, and we have the tools, the space, and the people to do it.

You are here at a particularly interesting and exciting juncture in medical research--a time when powerful and versatile techniques are available that can yield information on molecular structure and metabolic processes.

New means of non-invasive diagnostic testing and refinements in treatment techniques are making it possible to carry out an increasing proportion of clinical care and research on an outpatient basis. CT scanning spares the patient many of the invasive types of diagnostic procedures that had been necessary previously. PET--positron emission tomography--will allow us to follow the brain's metabolism and function in finer detail than was hitherto possible. MRI--magnetic resonance imaging--may be the most extraordinary and sophisticated tool of all. It promises to be the window through which we will be able to see molecular

structure and metabolic processes in previously inaccessible parts of the body.

We are challenged by the unprecedented rise of a new disease entity, acquired immune deficiency syndrome (AIDS), on which NIH is placing a very high priority in its intramural as well as extramural program. We know much more about AIDS than we did two-three years ago--about the characteristics of those at risk, about the probable mode of transmission, about the causative organism, and about the derangement of the immune function in these patients--but we still have a long way to go in devising possible therapy, and in developing an effective vaccine.

Many of you have chosen to work in the area of cardiovascular diseases. During the last 20 years, important advances in the treatment of myocardial infarction have gradually become standard clinical practice in hospitals throughout the world. The death rate for patients suffering MI has gone down, due to prompt expert pre-hospital coronary care, more accurate diagnosis, and more effective treatment, to which NIH scientists have made important contributions.

However, there is much to be done. New drugs for reducing the size of the thrombus within the coronary vessel are now being tested to determine whether they will lessen muscle damage and reduce the death rate. Other approaches to limiting the size of the damaged zone include the use of new drugs to reduce the oxygen needs of the endangered area, to improve blood flow through accessory coronary blood vessels, or to improve diffusion of metabolic fuels to the damaged zone. Clinical studies are now being



conducted to determine whether these drugs can indeed improve heart function and protect borderline areas of cardiac injury.

The rapid development of science makes it imperative that there be a continuing flow of new people educated and trained in the most modern concepts and techniques of science. To assure that scientists are able to recognize the potential clinical value of research findings, the number of medically trained individuals in the research pool must be continually replenished. The Medical Staff Fellowship Program offers young physicians and dentists this opportunity. [DSF and JBW in prototype program (started by Shannon) in NHI in 1953.]

Since the program began in 1985 with the appointment of 60 Medical Staff Fellows, then called Clinical Associates, it has grown steadily. It reached its peak in the period between 1965 to 1970 when the initiation of the Commissioned Officers Residency Deferment Program (CORD) allowed deferment of military service if a physician or dentist entered the Associate Program here at NIH. During those five years, NIH received more than 1,000 applications annually and from 166 to 226 appointments were made each year. In 1970 the CORD program was discontinued and the number of applicants dropped. In 1971 there were only 52 candidates selected. Since that time there has been a steady increase of applications for the Medical Staff Fellow appointments, as they are now called. This year there were 370 applicants, and 79 were selected for the 1985-86 program. [Total = 132, 42 schools.]

One of the striking features of the Medical Staff Fellowship Program is that it offers an exciting and stimulating medical



milieu in which free-ranging scientific inquiry in a setting devoted to the study of human disease provides a vigorous incentive to remain in the field. Many choose to remain at NIH for lifetime careers of fruitful research. As you progress through your training experience here, you will note that many of the senior people, some of them your preceptors, were themselves Clinical Associates. At NCI, Dr. Bruce Chabner, Director of the Division of Cancer Treatment, came here as a Clinical Associate. Dr. Robert Young, Chief of the Medicine Branch, was an Associate in 1967 and worked in the laboratory of Dr. Vincent DeVita, now the NCI Director. Dr. Philip Pizzo, Chief of the Pediatric Oncology Branch, came in 1973 as a pediatric fellow. He worked on Epstein-Barr virus studies and then began work on the infectious complications of cancer patients, which continues today. In the NHLBI, Dr. Bryan Brewer and Dr. Arthur Nienhuis were Associates. Dr. Steve Epstein came here in 1963 as an Associate and his first project was in the NHLBI exercise laboratory. Dr. Jesse Roth of NIADDK, noted for his research on diabetes and insulin receptors, began as a Clinical Associate in 1963. And I could name many, many more.

[Marginal Note: HHMI - 25 students]

So you can see that the Medical Staff Fellows provide much of the impetus to the research conducted here. Whether you choose to stay here as medical investigators or move to another medical center in this country or abroad, you will influence the course of medical research in the future, and your experience at NIH will have a profound influence upon you.

# THE FEDERAL-PRIVATE PARTNERSHIP IN AGING RESEARCH\*

by

James B. Wyngaarden, M.D.\*\*

In carrying out its mission, the National Institutes of Health (NIH) relies heavily upon cooperation with non-Federal institutions and individuals. Four-fifths of our total budget (currently over \$5 billion annually) is expended for the support of research in universities, medical schools and other health related laboratories. The partnerships developed and nurtured through our extramural programs have proved to be highly productive and beneficial to all parties.

Somewhat different but equally vital relationships exist between the NIH and the voluntary organizations concerned with specific areas of health problems and related research. The collaboration of the American Federation for Aging Research and the NIH is such a partnership.

On the surface it might appear that when the Federal Government appropriates large sums for the many facets of biomedical research, the need for voluntary support of research on the same subjects would be obviated. As we all know, such is not the case. The fact that the strengths and weaknesses of the partners are for the most part complementary, accounts in large measure for the vitality of the voluntary organizations whose missions intersect those of Federal agencies. In many such partnerships Federal dollars and private dollars are synergistic and the total benefit is greater than the sum of its parts.

Estimates of national expenditures for health related research and development in the United States during 1985 are expected to reach a total of about \$13.5 billion. It is predicted that voluntary health agencies and foundations will provide about \$240 million or a little less than 2 percent

---

\*Address at the American Federation for Aging Research Awards Luncheon, Sheraton Hotel, New York, NY., July 12, 1985.

\*\*Director, National Institutes of Health, Bethesda, MD.

of this total. In 1949, when the national expenditures for health research and development amounted to less than \$150 million, foundations and volunteers were responsible for about \$20 million or about 13 percent. In the intervening years, foundation and voluntary agency support has grown by a factor of ten, but the national total for research and development has grown almost a hundredfold, largely because of massive increases in research and development expenditures by the Federal Government and industry.

The impact of the research support provided by voluntary health agencies, however, has continued to be greater than the statistics would suggest. One reason for this disproportionate influence is the relatively narrow focus and concentrated mission of such agencies, as well as the flexibility enjoyed by many voluntary agencies in carrying out their programs. Within the general realm of biomedical research, the NIH has an extremely broad mission, and it must be concerned with the effect of changes in one program on others for which the agency has equal responsibility.

Furthermore, the NIH must be sensitive to the need for and apply the necessary safeguards required in the expenditure of public funds. For example, the NIH is bound by law to subject grant applications to specific review processes. For reasons of equity, public accountability and the maintenance of research quality, to say nothing of the law, we cannot short circuit the process that under normal circumstances requires from nine months to a year from the time a research application is received until it is funded.

Many investigators who have been able to turn to voluntary agencies for vital start-up or interim support have later become participants in major research programs sponsored by the NIH. Often the funds from the voluntary agency made a critical difference at a critical time--on occasion the availability of such funds was the thing that encouraged and enabled a promising investigator to continue his or her career.

Beyond the obvious advantage of being able to act quickly and flexibly, voluntary agencies have unique strengths because their memberships are



interested in the organization's purpose. In other words, they are volunteers. Whatever the mix of lay and professional members, voluntary health agencies are made up mostly of persons having an active interest in a particular facet of health.

It almost inevitably follows that when we invest time, energy and resources in a cause, we become more interested in it. Thus, the active members of voluntary agencies simultaneously demonstrate and enhance their level of interest when they work in behalf of such an organization. This fact has made voluntary agencies powerful and respected advocates. It is not necessary for an organization to be operated as a lobby group to have significant influence on decisions by Congress and the Administration. Watchers of the Washington scene are quick to point out that genuine grass roots involvement by appreciable numbers of supporters of a voluntary agency will not go unnoticed in the halls of Congress. Practically every page of the history of the development of the National Institutes of Health bears testimony to the constructive influence of voluntary health organizations and we continue to view the many groups having interest in our programs as valuable allies. But this focus on research and the Federal Government is only one aspect of the programs that voluntary agencies are uniquely effective in carrying out.

Through their informational programs, and even in the course of their fund-raising activities, America's voluntary health agencies have conducted highly effective health education programs. An example is the American Heart Association's current reminder campaign to reduce the risk of heart disease by dealing with high blood pressure, smoking, and high cholesterol levels. Similar programs and educational efforts in behalf of behavioral modification are considered to have been the powerful forces in the reduction of heart disease and stroke in this country that has been a spectacular achievement of the past two decades.

While mentioning the service of the American Heart Association, I would be remiss if I failed to mention the service to the AHA rendered over a 50-year span by your president, Dr. Irving S. Wright. He has told me



that AFAR is structurally modeled after the AHA, particularly in its commitment to raise funds for young investigators to keep them from leaving research for other fields.

This is the last forum in which I would venture to expound on any correlation between the youth of the investigator and his or her productivity. However, we must recognize the significance of the career commitments being made by young physicians and young scientists and what such decisions mean to the future of biomedical research.

Later this month, I will be participating in an Anglo-American conference to be held in London on clinical investigation of infectious diseases. The underlying theme of the meeting is concern that there appears to be a continuing decline in the number of physicians devoting significant portions of their careers to research on infectious disease.

The decline of interest in clinical research on infectious diseases is a manifestation of a general trend. A study by the NIH Division of Research Grants shows that the number of traditional research grants awarded to M.D.s fell from about 3,400 in 1968 to about 2,500 in 1973. There has been some recovery since that time, but ten years later the number of grants to M.D.s was below 3,000. This was happening at a time when there was a major increase in the total number of project grants awarded. NIH currently funds more than 17,000 investigator-initiated project grants as compared with about 10,000 in 1972. But Ph.D. investigators are almost entirely responsible for the increment in the number of grants since that time.

The decline in percentage of M.D. investigators working under project grants reflects in part the submission of relatively fewer grant applications by M.D.s. Another compounding factor is the intense competition. When one looks at the success rate of new applications alone, one finds that since about 1970 new M.D. applicants have competed less well than new Ph.D. applicants.

The simplistic explanation that greater difficulty is inherent in working with human subjects is probably not the entire answer to the lower

approval rates for physician investigators. Science has become complex, the methods intricate and the training period so long that the physician even after two or three years of fellowship training remains less well trained than the Ph.D. scientist who has been training for a research career since the baccalaureate degree. In my view, the trends of the past decade reflect the progressive professionalization of biomedical research, in particular of clinical research. I hope there will always be room for the creative amateur in clinical investigation, but history indicates that such a person is less likely to secure external support for his or her work. Success for an M.D. investigator is increasingly dependent upon substantial training in the information, concepts, and methodologies of complex modern science. To be a first-rate scientist and a well-qualified physician is a demanding calling.

Scientists committed to careers in gerontology and geriatrics with high competencies in various biomedical, behavioral, and social sciences are critical to advancing research in aging. Examples of the wide range of disciplines of importance in aging challenging both M.D.s and Ph.D.s are molecular and cellular biology, the neurosciences, immunology, endocrinology, psychology, sociology, health economics, and epidemiology.

While the support of the National Institute on Aging and several other public and private organizations, including AFAR, have increased the number of researchers in aging in recent years, available information indicates that the current cadre is well below half the recent estimates of minimum need. Such estimates were included in a special report to the National Institute on Aging in 1981 by the Rand Corporation that projected the number of research scientists needed to establish a sound nucleus of basic and applied scientific information in geriatrics. The estimates range from about 1700 to 2600 researchers. When we take into account the need for teaching as well as research in the fields of geriatrics and gerontology, it is estimated that we have only 10 percent of the trained personnel required.

In spite of this serious shortage, there are encouraging signs. For example, an increasing number of mid-level and senior researchers with experience in other areas are indicating interest in extending or shifting their focus of concentration to encompass aging issues. At the same time, a number of existing research and research training programs in related disease-oriented fields have indicated interest in adding geriatric training activities to their programs.

The 1986 budget request for the National Institute on Aging is now being considered by the Congress and I will not forecast the outcome. But it is noteworthy that the current research training programs are substantially larger than they were last year. In 1984, the research career and training programs of NIA were budgeted at a total of \$6,331,000. Currently, the budget for these programs is \$10 million. There are now 76 research career awardees as compared with 68 last year, and 221 full-time trainees in our National Research Service Award as compared with 161.

In noting hopeful signs, I would be remiss not to mention the activities of our voluntary partners, particularly the American Federation for Aging Research. Your organization has made a direct contribution to the nurture of interest in aging research by making limited amounts of funds available in a timely fashion to young researchers for support of their research initiatives. With experience and exposure to the broad vistas of research questions, some of these young investigators are certain to be launched into careers of accomplishment.



ADDRESS\*

by

JAMES B. WYNGAARDEN, M.D.\*\*

I am honored by your invitation to address this Plenary Session of the 13th International Congress of Gerontology and pleased to have this opportunity to discuss with you concerns and interests we hold in common.

As Director of the National Institutes of Health, the principal biomedical research agency of our Federal Government, I have special interest in the National Institute on Aging, our youngest major component. The National Institute on Aging was created in May 1974. Passage of the Research on Aging Act that established the Institute was the culmination of a twenty-year effort to gain governmental recognition and support for basic research on aging. At the forefront of the effort were organizations such as the Gerontological Society and mass membership organizations such as the American Association of Retired Persons--National Retired Teachers Association, and the National Council of Senior Citizens. The Research on Aging Act represented one of the first instances where scientific and senior interests worked closely toward a common goal. This collaboration resulted in a highly effective campaign both in Washington and at the grass roots level. A number of key individuals played a decisive role in securing passage of the Act. Any list of such individuals beyond the Congressional sponsors and proponents of the legislation would of necessity include Mrs. Florence Mahoney, the first person to organize support on Capitol Hill for a separate aging institute, and your current president, Dr. Busse, as well as two other past presidents of the Gerontological Society, Drs. Eisdorfer and Sinex. Their vision, drive, and determination set the pace for later constructive effort.

The legislative charter of the National Institute on Aging designated the Institute as the chief Federal agency responsible for promotion, coordination, and support of basic research and training relevant to the aging process and the diseases or problems of the elderly. The mandate of NIA is unique among the NIH institutes in a number of ways. For instance, it is charged by Congress to conduct research not only in the biological and biomedical sciences but also in the behavioral and social sciences.

The Institute came into being in the mid-1970's at a time when the total NIH research budget had reached a plateau. In spite of the

---

\*Presented at Plenary Session of XIIIth International Congress of Gerontology, New York, July 13, 1985.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



timing, however, the Institute's funding for basic research has increased more than eightfold, from \$7.6 million in 1976 to the 1985 level of \$72.3 million.

Permit me to point out a few facts for those of you not entirely familiar with the structure and mechanisms of the National Institutes of Health.

The agency is made up of 11 Institutes, the National Library of Medicine, and several specialized Divisions. Most of the Institutes were created to concentrate their efforts around specified disease families or organ systems; for example, the National Cancer Institute or the National Heart, Lung, and Blood Institute. We operate a large research program within the NIH, with more than 2,000 scientists actively engaged in our extensive laboratories and in our 500-plus bed Clinical Center and Ambulatory Care Research Facility. Of special significance to research on aging is an off-campus Gerontological Research Center in Baltimore.

Our in-house research program is large, but it represents significantly less than a fifth of our total research and research training activity. Eighty percent of the total NIH budget of over \$5 billion this year is expended through grants and contracts awarded to more than 1,200 academic institutions, hospitals, and laboratories in the United States as well as in other countries.

Over half of our entire budget goes to support research projects proposed by individual investigators. This mechanism is considered to be our most effective means for encouraging creativity. The response of the scientific community is such that even though our budget is substantial, we can fund only about a third of the meritorious applications, and consequently must make difficult choices among excellent proposals.

The quantity and the subjects of investigator-initiated research proposals provide an index of how the research community perceives scientific opportunity in various fields and disciplines.

That is why we feel it to be encouraging and significant that grant applications in the field of gerontology have more than tripled in number since 1976. Nearly 700 applications have been received by the NIA in the current year. Another example of increased interest in aging research is the number of trainees being supported under research training programs. Currently, 221 individuals are in the NIA training programs as compared with 151 in 1976. This roughly 50 percent increase happened when the total number of trainees supported by NIH decreased by about 7 percent.

During this decade, knowledge of the disease states common to the elderly and about the changes that occur with aging has improved significantly. Many important scientific questions, however, remain to challenge us. Continued research is needed to understand the mechanisms of aging and to understand the nature of age-associated diseases and disorders such as Alzheimer's disease and osteoarthritis.

This research is vital to assure rational and cost-effective plans for providing health care to our present and future elderly.

Research on Alzheimer's disease, the most common form of dementia among the aged, continues to be a high priority for the Institute on Aging as scientists and grantees attempt to identify what causes the disease and how it can be prevented or treated. An aggressive attack by the NIA on this devastating disease associated with old age has given hope that treatments may one day be available for those who suffer from this form of mental impairment. The establishment during 1984 of five centers for Alzheimer research provides a major step toward intensifying research on this important question. In our intramural Laboratory of Neurosciences based in the Clinical Center in Bethesda, the course of Alzheimer's disease and other dementias is being examined in patient volunteers with a variety of clinical test instruments including positron emission tomography (PET).

A workshop on molecular genetics, held in September 1984, urged increased attention to using molecular genetic techniques to study aging. This should provide insight into the mechanisms of aging and may permit a better understanding of age-related diseases. In the last few years, powerful new techniques have emerged in molecular biology.

In order to provide leadership in this field in our intramural program and to aid established laboratories in extending their research capabilities through the use of these new techniques, NIA is establishing an intramural Laboratory of Molecular Genetics. Research will be directed at examining changes that occur with aging in gene function and structure.

NIA's Baltimore Longitudinal Study of Aging has done much to improve our understanding of the aging process. This study, conducted by NIA's Gerontology Research Center, is in its 26th year for males and 6th year for females, and currently includes about 900 active participants. Among the significant results from this study during the past year is the finding that in persons who are free of any evidence of heart disease, there is no significant decline in maximum heart capacity with age. While there is a slower heart rate response to exercise stress, the older heart compensates by having a larger effective volume maintaining the same heart output.

A number of disorders and diseases that afflict older people and result in disability and institutionalization have received too little research attention from the medical community. These include the major types of functional disabilities such as incontinence, falls, and hip fractures. Through NIA's teaching nursing home program, support for clinical research in geriatrics is increasing dramatically. This NIA program has provided the example for private organizations to initiate programs involving a nursing home and medical school to examine basic clinical problems. While seven of these programs have been funded, 10 times that number of medical and nursing schools have begun collaboration with long-term care facilities.

Yesterday, I was privileged to address the American Foundation for Aging Research. I told them of a general concern within the biomedical research community over what appears to be a continuing decline in the number of physicians devoting significant portions of their careers to research. Over the past dozen years, there has been essentially no increase in the overall number of research grants awarded by the NIH to M.D.'s at a time when the number of such awards to Ph.D.'s has doubled. This situation is caused in part by a decline in the number of proposals submitted by M.D.'s. Furthermore, competition is much more intense now than it was a decade or so ago. When looking at success rates, one finds that since about 1970, new M.D. applicants have not competed as well as Ph.D.'s.

Science has become increasingly complex, the methods more sophisticated, and the training period so long that even after two or three years of fellowship training, the physician remains less well trained than the Ph.D. scientist who has been in research training since the baccalaureate degree.

Success for an M.D. investigator is increasingly dependent upon substantial training in the information concepts and the methodologies of complex modern science. I repeated to the Foundation group yesterday an observation whose validity is self evident: To be a first-rate scientist and a well-qualified physician is a demanding calling.

Scientists committed to careers in gerontology and geriatrics with high competencies in various biomedical, behavioral, and social sciences are critical to advancing research in aging. The wide range of disciplines of importance in aging challenge both M.D.'s and Ph.D.'s.

The need for clinically trained investigators in all areas of biomedical research is an international problem. I commend this challenge to the attention of this International Congress and its constituent organizations. For these challenges are universal in scope--there is a worldwide need for more knowledge about aging and for the development of a knowledge base that will distinguish between normal aging and disease states that may or may not be associated with aging.

More must be known about the health, social, and environmental factors that promote the independence, well-being, and effective functioning among the elderly worldwide so that reliable data can be used to determine present and future needs for the growing populations of older persons. An epidemiological approach, possible only through international collaboration, can provide an understanding of the determinants of ill health among the elderly and provide the bases for scientifically sound health policies.

Various National Institute on Aging programs are developing complementary studies to understand trends and cross-national variables in patterns of morbidity and cause-specific mortality, especially as they affect persons over 85, the fastest growing segment of the developed world. Scientists from other countries supported by the NIA



and U. S. investigators working with European scientists are studying Alzheimer's disease. NIA promotes international collaboration in geriatrics and gerontology through exchanges among individual investigators, development of studies related to program objectives, and cooperation with non-government and multilateral organizations. Its role as a collaborating center of the World Health Organization has been extended under a renewed agreement based upon research on health of the elderly.

Occasionally, one hears an optimistic statement regarding the disease-specific institutes of the NIH that their basic purpose is to "succeed themselves out of business." An example of such success would be to find a fully effective means for preventing a disease so that the need for further research on the target disorder would be minimized.

Whatever the real merit of this statement, it definitely is not applicable to the National Institute on Aging. It takes no prophet to foresee the increased demand for persons with knowledge and skills in both geriatrics and gerontology to help care for the growing elderly population. Enormous benefits can be realized from research that leads to more effective methods of disease and disability prevention and care for the aging and the aged.

By continuing to support and conduct research aimed at improving the quality of life for the elderly, we will be promoting changes that will improve the quality of life and sense of well-being of all ages. The aging research of today will undoubtedly help bring about the changes that will benefit all mankind in the future.

X X X X





"RESEARCH IN THE USA"\*

by

James B. Wyngaarden, M.D.\*\*

The comprehensive subject "Research in the USA" provides me unusual latitude to range over such topics as advances in science, government involvement in research, education, and a variety of other matters. However, in the context of the rich scientific exchanges that have been taking place here this week, I will confine my discussion largely to a sketch of organizational aspects of the biomedical science establishment in the United States--to comments on the trends in funding for research by the Federal Government, by industry, and by other interests, and to an examination of our concerns about the need for more well-trained clinical investigators.

First, permit me to sketch a panorama of national support for health research and development in the United States. Our most recent projection of total national expenditures for health research and development during 1985 is about \$13.5 billion. The Federal Government is expected to be the source of just over one-half of the total or about \$6.8 billion. The National Institutes of Health alone will provide \$4.8 billion or 70 percent of the total Federal investment in biomedical research. The NIH provides over 35 percent of the funding from all sources in the Nation.

During the past decade there has been a sizable increase in the share of research supported by industry. Ten years ago, industry's expenditures in the United States for health research

---

\*Presented at the Royal Society of Medicine Anglo-American Conference on Clinical Investigation of Infectious Diseases, London, July 24, 1985.

\*\*Director, National Institutes of Health, Bethesda, Maryland.

and development amounted to \$1.3 billion, about 27 percent of the Nation's total. In 1985, industry is expected to spend about \$5 billion, or 37 percent of the national total, slightly more than the share supported by the NIH. That, by the way, is a change, for until two years ago, NIH expenditures had exceeded industry's total annually since World War II. It is worth noting that increased expenditures by industry are accompanied by new kinds of relationships between some of our finest academic institutions and the industrial organizations. Ingenious contractual arrangements have been developed to protect the interests of both industry and academia, with special attention to such essentials as freedom of inquiry and open scientific communication.

There is much to be gained by all concerned in these new modes of cooperation. While the NIH has not interposed itself into these joint enterprises, we have deep and continuing interest in them and in their success.

Our agency's keen interest in the status of institutions of higher learning is more than general concern for the good of science. NIH research programs are rooted deeply in academic institutions, especially schools of medicine. Within this year, more than 80 percent of the total NIH budget of over \$5 billion will be awarded to academic institutions, hospitals, and a variety of laboratories for the support of biomedical research. Half of those awards will be made for the support of research conducted at medical schools.

At the NIH, our prime instrument for the support of biomedical research is the project grant awarded in response to investigator-initiated proposals. In most instances, these investigators are members of the faculty or affiliated staff of medical schools. A little over half of the total NIH budget, or more than \$2.5 billion, is expended for such grants. Through this mechanism and other extramural programs, the NIH currently is responsible for the deployment of about 50,000 scientists, at least part-time, in pursuit of projects initiated within the

scientific community--projects evaluated for scientific merit by panels of non-Federal peer reviewers. The mechanisms employed by the NIH have served well our goal of securing the maximum involvement of our country's scientific community in creative biomedical research.

In one area, however, we have found it difficult to fulfill increasing research needs. The number of optimally trained physician/investigators has not kept pace with the field. Physician/investigators have special insights to offer and in some instances they are absolutely essential to the conduct of needed research studies.

To identify some of the reasons for the situation in which we find ourselves, it is helpful to review some historical currents in science and medicine.

In the past half century, a revolution has taken place in biology--a revolution so sweeping in its scope as to transform our understanding of all living things. In little more than a generation, the scientific community has witnessed the development of what has been called "a coherent, if preliminary, outline of the nature of life."<sup>1</sup>

The explosion in knowledge has brought new vigor into practically every branch--every discipline--of the science of biology and, at the same time, has created new branches. The expansion and branching, surprisingly, have not resulted in the fragmentation that one might expect but rather has fostered a kind of convergence.

Nobel Laureate Arthur Kornberg perceived this paradox and captured its significance in a brief paragraph. He noted the extraordinary recent developments in genetic chemistry and immunology but asserted that ". . . there is an even more profound development in medical science, a change that is truly revolutionary and yet one never hears it mentioned." That development, he said, ". . . is the confluence of the many discrete and previously unrelated medical science subjects into a single unified



discipline. Anatomy, physiology, biochemistry, microbiology, immunology, and genetics have now been merged and are expressed in a common language of chemistry." He maintained that "By reducing structures and systems to molecular forms, all aspects of body form and function blend into a logical framework."<sup>2</sup>

In the functional realm of clinical application, however, the growth of knowledge has been accompanied by a kind of divergence that seriously affects our resources of clinical investigation. The division does not occur along disciplinary lines but happens in response to the circumstances that seem to force some of our brightest young men and women to make sharply delineated "either/or" choices--to choose whether to practice medicine or to conduct research.

Not long ago, in simpler times, the well-trained physician was expected to combine research with medical practice. Physicians who applied scientific techniques to their observations and investigations in the course of diagnosis and treatment were rewarded with dividends of new medical knowledge. The works of the great pioneers, Koch, Pasteur, and Lister, were extended and amplified through the experiments and insights of such individual physicians. During the last three decades of the nineteenth century, young Americans trained in medical care and medical research were returning home from Europe filled with enthusiasm about the progress made possible by the findings of the giants of European science. It was during this period that modest beginnings were made in establishing laboratories in the United States dedicated to biomedical research. One such laboratory, a part of the Marine Hospital Service in New York, much later became the National Institutes of Health. We will celebrate our centennial in 1987.

Early in the twentieth century, several of the major medical schools in the United States began to change their orientation from exclusive preoccupation with medical practice to a strong and enthusiastic emphasis on research, including the basic sciences. During World War II, our medical schools served the national

interest both as a source of needed medical manpower and as productive biomedical research laboratories. In the post-war period, the national interest in supporting medically related research was intensified while at the same time the numbers of medical schools were growing. Research was fully integrated into the programs of most schools. By 1960, Federal support for research was the largest income item in the budget of most American medical schools. In the past decade, income from patient care by faculty members has surpassed research dollars as the principal source of funding for the operations of medical schools.

More than half a century has gone by since the majority of medical schools began to devote substantial resources to biomedical research. The close and essential relationship has continued greatly to the enhancement of the quality of education as well as to the advancement of knowledge.

However, for the individual men and women at various stages in their training to be physicians, the distinction seems to be more sharply drawn than before between research and the practice of medicine. This divergence does not bode well for the future of research nor does it augur well for patient care. Dr. David A. Hamburg, former President of the Institute of Medicine of the National Academy of Sciences, sounded the warning five years ago that "We must do everything in our power to see that the great fundamental advances--indeed the inspiring advances in molecular and cellular biology--will be available as soon as possible for health interventions of a demonstrably useful character. But the authentic biological revolution that has been generated by several decades of intensive basic research is not easily translated into clinically valid applications. An interpreter is needed and it is the clinical investigator who serves that function. The flow of information is by no means unidirectional; if basic science has something to say to clinical investigation, so too does clinical investigation offer much to basic science. Clinical research remains the vital bridge between advances in basic science on the

one hand and improvements in health care--diagnostic, therapeutic, or preventive--on the other."

Dr. Hamburg went on to say, "I was concerned in 1975 and remain concerned today that the interwoven fabric of basic science and clinical investigation is to some extent unraveling."<sup>3</sup> I share Dr. Hamburg's concern. We need to look at a number of factors that appear to be contributing to a declining interest in clinical investigation on the part of young physicians.

The absolute number of NIH traditional research grants awarded to M.D.s fell from about 3,400 in 1968 to about 2,500 in 1973. There has been some recovery since, but the number was still below 3,000 in 1983. NIH currently funds more than 16,000 R01 type research grants, compared with 9,000 in 1972. The increment has gone almost entirely to Ph.D. applicants. Accordingly, the percentage of NIH research grants held by M.D.s has fallen progressively over the years. In 1960, M.D.s held about 45 percent of all NIH grants; currently, M.D.s hold only about 22 percent.

The decline in percentage of M.D. investigators working under project grants reflects in part the submission of relatively fewer grant applications by M.D.s. In 1970, for example, M.D.s comprised about 30 percent of the applicants; by 1980, only 24 percent. Another important factor is the intense competition. When one looks at the success rate of new applicants alone, one finds that for the past 15 years, new M.D. applicants have competed less well than new Ph.D. applicants, with both groups competing less successfully than the M.D./Ph.D. applicant.

The simplistic explanation that greater difficulty is inherent in working with human subjects is probably not the answer to the lower approval rates for physician investigators. Science has become complex, the methods intricate, the training periods so long that the physician, even after two or three years of fellowship training, remains less well trained than the Ph.D. scientist who has been training for a research career since the



baccalaureate degree. In my view, the trends of the past two decades reflect the progressive professionalization of biomedical research, in particular of clinical research. I hope there will always be room for the creative amateur in clinical investigation, but history indicates that such a person is less likely to secure external support for his or her work. Success for an M.D. investigator is increasingly dependent upon substantial training in the information concepts and methodologies of complex modern science. To be a first-rate scientist and a well-qualified physician is a demanding calling.

Programs have been launched in our country by the government, by industry, by voluntary health organizations, and by philanthropic foundations for the purpose of increasing the number of well-trained clinical investigators. Several of these initiatives are based on the observation that most medical schools' curricula provide little or no laboratory experience that is representative of modern day medical sciences. The rise of specialty fields and the lengthening of postdoctoral training programs have extended the clinical training necessary for board certification. The requirements of many certification boards are to a considerable degree inflexible and do not encourage the potentially creative physician to enter research training.

At the undergraduate medical school level, the NIH gives its Medical Scientist Training Program (MSTP) top priority in our training portfolio. This program is supported at a limited number of institutions that have a history of high academic performance and research productivity to train individuals for both the M.D. and the Ph.D. degree. Seventy percent of the graduates of this six-year program hold positions in medical schools, performing research, and engaging in the training of students and other physicians. We currently are supporting about 682 students at 25 institutions under this program. The NIH also has a number of programs that provide support for early student exposure to research careers during the summer months or in off quarters.



An innovative addition to NIH program resources is the joint NIH-Howard Hughes Medical Institute Scholars Program. In this activity, whose purpose is to attract medical students into research, the Howard Hughes Medical Institute will support the research training of 25 to 30 medical students at NIH for from nine months to a year following their second year in medical school. The joint agreement provides for funding by the Hughes Institute for stipends and travel expenses for the trainees who will participate in research activities in our intramural laboratories side by side with some of NIH's leading scientists. The Hughes funding will also make possible the renovation of a structure on the NIH campus into living quarters, classrooms, and teaching laboratories. The first class of 25 students, selected during the spring in nationwide competition, will begin training at NIH in September of this year.

Other of our training programs are intended for physicians who have completed medical school and several years of clinical training without any special research experience. Most such physicians are unprepared for research. Even where they might have participated successfully in one or more research projects, the experience does not substitute for a planned program to develop research expertise. A series of NIH awards, called Research Career Development Awards (RCDA), has been developed for physicians in this situation. The oldest of these is the award solely for salary and fringe benefits. More than 80 percent of those who received RCDAs in the past now have support for a research project grant. Similar awards include an academic investigator award, the clinical investigator award, the mid-career development award, and the physician-scientist award. These provide salary and fringe benefit support, and some laboratory support for periods of 3-5 years of training, often with several years of basic science experience before entering clinical research. These reflect my belief that the traditional training grant to a division or department, which normally provides 2-3

years of training much diluted with clinical duties and ambiguous goals including subspecialty qualifications, is outmoded.

A number of foundations, industrial organizations, and voluntary health organizations have developed fellowship programs and awards for physicians encouraging or assisting them in careers of clinical research. Such awards usually specify that 90-100 percent of supported time be devoted to research. These physicians will pursue independent projects in U.S. medical schools in infectious diseases, cardiovascular medicine, diabetes, rheumatology, and biological psychiatry.

All of these efforts are constructive and we believe will be effective in increasing the essential participation by physicians in biomedical research.

The auditorium of the NIH Clinical Center has a quotation carved in the marble wall of its entrance, a quotation from the Center's first Director, Dr. Jack Masur, for whom the auditorium is named, that captures this concept of mutual enhancement. It reads, "Hospitals with long traditions of excellence have demonstrated abundantly that research enhances the vitality of teaching; teaching lifts the standards of service; and service opens new avenues of investigation."



180

**REMARKS\***

by

James B. Wyngaarden, M.D.\*\*

Our ability to serve the high purposes of this agency depends upon the joint effort of personnel with a very great variety of skills. We are, in fact, a small city whose parts work well individually and collectively.

At times, however, we are especially dependent upon the successful efforts of one segment or another of our community. A little over a month ago such a time was upon us when about a hundred animal rights activists occupied the eighth floor of Building 31A. Suddenly, personnel of the Division of Safety, and especially the NIH Police, were confronted with a test of their professionalism, their good judgment, their skill, and, as hours and days went by, their patience and restraint.

Dr. Barkley, you, Captain Davenport, and your colleagues passed all these tests brilliantly. It is not surprising to us that you did so well -- and speaking on behalf of NIH as a whole I wish to express our sincere gratitude. A special, and personal, expression of thanks is stated by the presence of many members of the NINCDS staff who themselves are due much credit for the way they faced and gracefully endured a difficult time.

For them and for the rest of us, let me say to our honored guests--the NIH Special Police--that we hope by this little ceremony to show in a small way our pride and appreciation for what you have done.

---

\* At reception for NIH Special Police and those involved in protecting NIH and the NINCDS employees at the time of the Building 31 demonstration by the Animal Rights activists, Building 1, Wilson Hall, August 19, 1985.

\*\* Director, National Institutes of Health, Bethesda, Maryland.





ADDRESS\*

by

James B. Wyngaarden, M.D.\*\*

I am very happy to join you today during this meeting of the Hartford Foundation Scholars Program. When he invited me to attend, Dr. Rosenberg left open to me the choice of subject matter. I thought it would be appropriate for me to talk briefly about the Federal commitment to the renewal of the Nation's pool of biomedical scientists, particularly to the training and development of physician-scientists.

Although some of the past and present Hartford Scholars and the Advisory Committee members no doubt are familiar with the National Institutes of Health (NIH) programs, it might be useful and interesting to review the evolution of our commitment to training and mention the current opportunities and challenges that lie before us. As you may know, the training of young investigators has been a long standing interest and commitment of mine, even before I became NIH director.

The NIH will soon observe its one hundredth anniversary. Thus, the history of the organization has become of special interest, and I hope you will permit a brief excursion into the past. We trace our origins to 1887 to the Hygienic Laboratory located in the Marine Hospital on Staten Island, where a few hundred dollars were initially spent in setting up a small facility for the conduct of medical research, aimed particularly at the study of cholera, yellow fever, and other infectious diseases that were major public health problems of that period.

It was not until just after World War II that we saw the development of what might be called "the modern NIH"--when the Nation's response to the challenges of the war effort brought about the formation of productive

---

\*Address given at the Hartford Foundation Scholars Program,  
New York, New York, September 7, 1985.

\*\*Director, National Institutes of Health, Bethesda, Maryland

partnerships linking the government with both academic institutions and independent laboratories for the conduct of biomedical research. In response to the sudden need for additional knowledge on how to deal with the health problems of the armed forces, the military had little choice but to turn to established non-Federal laboratories for the conduct of vital studies.

Since that time NIH has proceeded on a course that, in many ways, was charted by a report written in 1945 by Vannevar Bush, the President's science advisor, which greatly influenced congressional action in the immediately succeeding years. This report, SCIENCE--The Endless Frontier, outlined policies for Federal support of health research that have served the national interests so well since that time. The flavor and substance of the document stand up in steady perspective when viewed with the critical hindsight of 40 years. I would like to read a few sentences from it:

"The publicly and privately supported colleges, universities, and research institutes are the centers of basic research. They are the wellsprings of knowledge and understanding. As long as they are vigorous and healthy, and their scientists are free to pursue the truth wherever it may lead, there will be a flow of new scientific knowledge."

Thus, back in 1945 Vannevar Bush acknowledged the necessity for a Federal Government-academic partnership in the pursuit of excellence in biomedical research.

Vannevar Bush was emphatic on the importance of manpower development. On page three of his nearly 200-page report he wrote:

"The responsibility for the creation of new scientific knowledge--and for most of its application--rests on that small body of men and women who understand the fundamental laws of nature and are skilled in the techniques of scientific research. We shall have rapid or slow advance on any scientific frontier depending on the number of highly qualified and trained scientists exploring it."

This was the foundation for the "modern NIH," which blossomed under Dr. James A. Shannon, an unusually strong leader who became director in 1955. At that time the total NIH budget was \$82 million, and the public mood was ripe for rapid and massive expansion of the NIH and its programs. When he retired as director, 13 years later in 1968, the NIH budget had passed \$1 billion. During Dr. Shannon's directorship the basic mechanisms of support of biomedical science were established, and these have continued to serve us well.

Jim Shannon set about building the research capability of this country, both through the intramural program at Bethesda and through substantial expansion of the mechanisms of grants-in-aid to institutions. Corollary objectives included strengthening the institutions in which biomedical research would be done, and development of training mechanisms that would ensure a continuing supply of competent scientists drawn from the best and brightest young minds in the universities. The programs of the NIH were to modify the topography of the academic medical center, directly influencing--and most of us would say greatly strengthening--medical education. Thus, Dr. Shannon expanded the partnership theme of earlier days and added to it the idea of NIH's responsibility for reinforcing and nurturing the academic institutions in their pursuit of biomedical knowledge.

The NIH support of training followed a similar historical pattern. The NIH has supported research training programs since 1937, when authority for the training of biomedical researchers was first provided to the National Cancer Institute. In the 1950s, when institutional training grants were first established their primary purpose was to build the capacity of the U.S. health research institutions for providing trained individuals to utilize the then ever growing amounts of money available for biomedical research. The need was so great in many instances that those specialties which did not attract enough people to satisfy health care needs, much less research needs, were provided with training monies for residences. Few, if any, restrictions were placed on the appointment of trainees, with the rationale that if enough fertilization took place, some would survive to do research. There were no restraints on duration of



trainee appointment. There was little prescribed relationship between the institutional support requested in the training budget--to provide the necessary environment to develop investigators--and the number of trainees to be supported.

But this was to change in the 1970s. Following intense conflict between the administration--which declared in 1973 that public monies should not support research training--and the universities, the authority for research training under the Public Health Service Act was abolished. In 1974, after two years of a seriously curtailed interim program, the National Research Service Award Act (NRSA) was passed. In addition to a payback obligation the NRSA included a number of other constraints. Research training was permitted only in areas of national need--defined by a National Academy of Science continuing study--and there was a restriction on the time during which an individual could receive NRSA support. Furthermore, the Act mandated that no less than 25 percent of the total appropriation must be awarded as individual fellowships. The PHS further ruled that only 25 percent of the total grant could be used for enrichment of the training environment at the institution. (Since then, the legislation has been softened by succeeding amendments, but the deemphasis on institutional training environment has been further underscored--institutional costs of research training have now been reduced to approximately 11 percent of the award.)

During this period of readjustment of NIH training support and budgetary stringencies, the numbers of trainees and fellows began to decrease: in 1969 there were more than 16,000 full-time trainee years in our programs, dropping to 12,272 in 1975, the year following the inception of the new NRSA program. For the past five years the number of budgeted training positions has been level at approximately 10,000.

, Although the NAS has noted the special need for training clinicians in research in its 1983 report, and recommended that 2,800 such individuals be trained each year, we have been working very hard to attain that many M.D.s on NIH traineeships. In 1970 there were approximately 4,700 clinical postdoctoral fellows in research training positions, a figure which had

fallen to approximately 1,800 individuals in 1978, some 1,000 short of that year's NAS recommendation. While this probably represents to a large extent the disappearance of the purely clinical trainee, there is no question that the payback requirement and many other factors, societal and economic, have been discouraging young physicians from seeking research training toward a career in research.

While the NRSA was having specific effects on the training of young researchers, this was only a part of greater economic influences in operation. As early as 1974, the NIH had begun accommodating to a relatively constant budget by funding the cream of an increasing number of excellent research proposals through shifting funds from among various other program mechanisms. By 1975, the NIH appropriation had just reached \$2 billion, but the positive slope of the growth curve was flattening noticeably.

From this early readjustment grew an NIH policy termed stabilization, in which investigator-initiated research projects and research training have been given top priority. Each year, since the articulation of this policy in 1980, NIH has endeavored to fund a minimum of 5,000 new and competing renewal awards and to support a minimum of 10,000 trainees. This stabilization policy makes a powerful statement to the extramural community. It says that NIH is doing its utmost, consistent with program balance and congressional mandates and directives, to assure that the best research will be adequately funded, and that young scientists will have opportunities in research. The President's signing last month of the Supplemental Appropriations Act of 1985 cleared the way for NIH to fund 6,200 new and competing grants in Fiscal Year 1985. Although this represents the mandate of the Congress and a gain over the 5000 originally sought by the administration, it seems likely that FY 1986 levels will be substantially below 6000 awards.

Although the stabilization of research project support has received most attention over the past five years, our commitment to research training has always been a part of our stabilization effort--simply because of our view--advanced by Vannevar Bush in 1945--that training and research programs

are so closely interwoven as to be practically indivisible. In the coming years, we expect to continue to fund about 10,000 trainees annually.

What must be underscored in my brief review of the ebb and flow of Federal support for biomedical research and training is that it has been remarkably successful. The biological revolution spawned over the past forty years of our partnership with academia is far from over and, in fact, is beginning to approach major questions with immediate relevance to human health. Because many of the understandings gained from the age of molecular biology are now beginning to move toward clinical application, it is obvious that we will need a steady supply of well-trained physician-scientists to help in the incorporation of this new knowledge into the working motifs of medicine.

Given the rapid pace of advancement in research, the task of keeping abreast is growing more and more difficult for clinicians. Science has become complex, the methods intricate, and the required training long. The explosion of biomedical knowledge in the past decade has forced the progressive professionalization of biomedical research, in particular clinical research. I hope there will always be room for the creative amateur in clinical investigation, but recent history indicates that such a person is less and less likely to secure external support for his or her work.

Success for an M.D. investigator is increasingly dependent upon substantial training in the concepts and methodologies of complex modern science. To be a first-rate scientist and a well-qualified physician is a demanding calling.

The importance of more and better quality training for our future physician-scientists cannot be overemphasized. Recent analysis by NIH has indicated that as far as M.D. postdoctoral trainees are concerned, the longer they have trained, the more likely they are to apply for and receive an NIH grant. Unless they have a minimum of three years in research training, they usually are not successful in competing for grants.



Fortunately, there is a great deal of interest in this country--expressed by the Administration, by the Congress, and by the scientific community--in finding means to provide for future clinical investigators. Programs have been launched by the government, by voluntary health organizations, and by philanthropic foundations--notably the Hartford Foundation--for the purpose of increasing the number of well-trained clinical investigators. Private foundations and voluntary agencies make a large commitment to developing the capacities of the country's physician-researchers. A recent survey (conducted by RAND for the Hartford Foundation), giving a probably conservative figure, estimates that all private groups provided roughly 275 stipends for research development and 125 starter grants to young physicians during 1981. The Hartford Fellowship makes a substantial contribution, particularly because it is restricted to M.D.s and, unlike many of the private programs, unrestricted by field.

For its part, the NIH has an array of training and career development programs that are especially designed with M.D.s in mind. We give the Medical Scientist Training Program (MSTP) top priority in our training portfolio. The MSTP program is supported at a limited number of institutions that have a history of high academic performance and research productivity to train individuals for both the M.D. and the Ph.D. degree. Seventy-six percent of the graduates of this six-year program hold positions in medical schools, performing research and engaging in the training of students and other physicians. We currently are supporting 682 students at 25 institutions under this program. The NIH also has a number of other programs under the NRSA that provide support for early student exposure to research careers during the summer months or in off-quarters.

An innovative addition to NIH resources is the joint NIH-Howard Hughes Medical Institute Scholars Program. In this activity, whose purpose is to attract medical students into research, the Howard Hughes Medical Institute (HHMI) will support the research training of 25 to 30 medical students at NIH for from nine months to a year following their second year in medical school. The first class of students, selected through nationwide competition, will begin training at NIH this month.



Other of our training programs are intended for physicians who have completed medical school and several years of clinical training without having had significant research experience. Most such physicians require extensive additional training to become successful investigators. Even where they might have participated successfully in one or more research projects, the experience does not substitute for a planned program to develop research expertise. A series of NIH awards, called Research Career Awards, has been developed for physicians in this situation. The oldest of these is the RCDA award solely for salary and fringe benefits. More than 80 percent of those who receive RCDAs also have support for a research project grant.

Other awards in the series include the Academic Investigator Award, the Clinical Investigator Award, the Mid-Career Development Award, and the new Physician-Scientist Award, which is most like the Hartford Foundation model. These provide a salary and fringe benefit support, and some laboratory support for periods of 3 to 5 years of training, undiluted with clinical duties and the ambiguous goals of subspecialty training. Often these programs offer several years of basic science experience before entering clinical research.

But, of course, the Federal Government--especially in times of stringent budgets--cannot bear full responsibility for nurturing the biomedical research enterprise in this country. Therefore, it is extremely gratifying that the private sector--including industry and foundations such as the Hartford Foundation--have come forward to participate in this effort to enhance training opportunities in academic institutions, particularly in the important area of clinical investigation.

I congratulate the Hartford Foundation on the leadership it has displayed in this important endeavor.

WELCOMING REMARKS TO THE SECRETARY\*

by

James B. Wyngaarden, M.D.\*\*

We are very pleased to have Secretary Heckler join us today for the start of the Consensus Development Conference on Adjuvant Chemotherapy for Breast Cancer. The Secretary has visited the National Institutes of Health several times in the past, showing her support for NIH programs and activities. She has been particularly interested in the programs of the National Cancer Institute, and in March of 1984 announced here at NIH the start of the Cancer Prevention Awareness Campaign, which is designed to help make the American public more aware of how they can reduce their risk of getting cancer. This consensus conference concerns itself with another of Secretary Heckler's abiding special interests--that is, women's health issues.

On behalf of NIH, the National Cancer Institute, and the Office of Medical Applications of Research, I want to welcome the Secretary to NIH and to our conference.

Madame Secretary.

---

\*On the Occasion of the Consensus Development Conference on Adjuvant Chemotherapy for Breast Cancer, Masur Auditorium, September 9, 1985.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



## "THE ROLE OF GOVERNMENT SUPPORT IN BIOMEDICAL RESEARCH"\*

BY

JAMES B. WYNGAARDEN, M.D.\*\*

IT IS A PRIVILEGE TO HAVE BEEN INVITED TO JOIN THIS DISTINGUISHED PANEL IN HONORING JACQUES GENEST. FOR ALL IN ATTENDANCE AND THOSE WHO MAY LATER USE THE PUBLISHED PROCEEDINGS, THIS INTERNATIONAL SYMPOSIUM OFFERS AN UNUSUALLY RICH ASSEMBLAGE OF PRESENTATIONS AND SPEAKERS. IT IS A FITTING TRIBUTE TO OUR HONOREE WHOSE EXTENSIVE CONTRIBUTION TO SCIENTIFIC LITERATURE CONSTITUTES A TREASURE IN ITSELF. PARTICULARLY VALUABLE ARE HIS INSIGHTS LEADING TO A BETTER UNDERSTANDING OF THE UNDERLYING CAUSES OF HYPERTENSION, AND HIS WORK GOES ON. I HAVE BEEN TOLD OF HIS RECENT RESEARCH INTEREST IN ATRIAL NATRIURETIC FACTOR (ANF) AS A REGULATOR OF BLOOD PRESSURE. THIS REMINDED ME THAT IN OUR REPORT TO CONGRESS THIS YEAR AT THE TIME WE WERE JUSTIFYING OUR BUDGET, WE HIGHLIGHTED SIMILAR RESEARCH. WE TOLD OF OUR INTEREST IN THE FUNCTIONS THAT CERTAIN HORMONES, PARTICULARLY ANF, MAY HAVE IN THE REGULATION OF BLOOD PRESSURE, BLOOD VOLUME, AND THE UTILIZATION OF SODIUM. AND THOUGH OUR EFFORTS AND THOSE OF DR. GENEST ARE PURSUED SEPARATELY, IT IS GRATIFYING THAT OUR SCIENTISTS AND GRANTEES ARE WORKING SIDE BY SIDE WITH HIM IN THIS NEW AREA OF EXPLORATION.

IN ADDRESSING MY ANNOUNCED SUBJECT, "THE ROLE OF GOVERNMENT SUPPORT IN BIOMEDICAL RESEARCH," I WILL REFER PRINCIPALLY TO THE

---

\*ADDRESS GIVEN AT THE INTERNATIONAL SYMPOSIUM IN HONOR OF JACQUES GENEST, SEPTEMBER 23, 1985, IN MONTREAL, CANADA.

\*\*DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MD



RESEARCH AND RESEARCH TRAINING ACTIVITIES OF THE NATIONAL INSTITUTES OF HEALTH. BEFORE DOING SO, HOWEVER, I WILL MENTION ONE NIH PROGRAM CENTERED ON HYPERTENSION, A PROGRAM WHOSE MAJOR PURPOSE LIES OUTSIDE THE NORMAL REALM OF RESEARCH. ALTHOUGH THE NATIONAL HIGH BLOOD PRESSURE EDUCATION PROGRAM DIFFERS IN NATURE AND METHOD FROM MOST OF OUR AGENCY'S ACTIVITIES, IT HAS BEEN HIGHLY SUCCESSFUL. BASICALLY ITS PURPOSE HAS BEEN TO STIMULATE BETTER HIGH BLOOD PRESSURE CONTROL BY INFORMING AND EDUCATING THE PUBLIC AND THE MEDICAL PROFESSION ABOUT THE SERIOUS HEALTH CONSEQUENCES OF HYPERTENSION AND THE BENEFITS ASSOCIATED WITH ITS EFFECTIVE CONTROL. WITH A COMPARATIVELY LIMITED INVESTMENT OF FEDERAL FUNDS, THE PROGRAM HAS EXERTED A SIGNIFICANT POSITIVE EFFECT ON THE PROBLEM OF HIGH BLOOD PRESSURE. ONCE THE PROGRAM WAS UNDERWAY, SIGNIFICANT PORTIONS OF ITS ACTIVITIES WERE CARRIED OUT BY VOLUNTARY HEALTH ORGANIZATIONS, PRIVATE INDUSTRY, AND PRIVATE HEALTH CARE ORGANIZATIONS, WITH NIH SERVING PRIMARILY IN A COORDINATING ROLE. TODAY THE PROGRAM ENCOMPASSES ALL 50 STATE HEALTH DEPARTMENTS, OVER 150 VOLUNTARY HEALTH AGENCIES, AND MORE THAN 2,000 COMMUNITY BLOOD PRESSURE CENTERS.

IN ADDITION, THE NIH SUPPORTS CLINICAL TRIALS INVOLVING THE TESTING OF DIRECT INTERVENTION METHODS TO LOWER HIGH BLOOD PRESSURE AND PREVENT HEART ATTACKS AND STROKE. FURTHER, THE NIH ALSO SUPPORTS DEMONSTRATION AND EDUCATION PROGRAMS USING METHODS THAT WERE SUCCESSFUL IN CLINICAL TRIALS.

IT SEEMS OBVIOUS THAT SUCH RESEARCH AND EDUCATIONAL EFFORTS BY MANY DIFFERENT GROUPS AND INDIVIDUALS FOR THE CONTROL OF HYPERTENSION MUST HAVE HAD A CONSIDERABLE PART TO PLAY IN CAUSING THE MARKED DECLINE OVER THE PAST DECADE OR MORE IN THE RATE OF MORTALITY FROM HEART ATTACKS AND STROKES.

BUT I WAS INVITED TO PRESENT A GENERAL DISCUSSION OF THE ROLE OF GOVERNMENT SUPPORT IN BIOMEDICAL RESEARCH. IN DOING SO, I WILL DIRECT MY REMARKS LARGELY TO A SKETCH OF ORGANIZATIONAL ASPECTS OF THE BIOMEDICAL SCIENCE ESTABLISHMENT IN THE UNITED STATES--TO COMMENTS ON THE TRENDS IN FUNDING FOR RESEARCH BY THE FEDERAL GOVERNMENT, BY INDUSTRY, AND BY OTHER INTERESTS, AND TO AN EXAMINATION OF CONCERNS ABOUT THE NEED FOR MORE WELL-TRAINED CLINICAL INVESTIGATORS.

FIRST, PERMIT ME TO SKETCH A PANORAMA OF NATIONAL SUPPORT FOR HEALTH RESEARCH AND DEVELOPMENT IN THE UNITED STATES. OUR MOST RECENT PROJECTION OF TOTAL NATIONAL EXPENDITURES FOR HEALTH RESEARCH AND DEVELOPMENT DURING 1985 IS ABOUT \$13.5 BILLION. THE FEDERAL GOVERNMENT IS EXPECTED TO BE THE SOURCE OF JUST OVER ONE-HALF OF THE TOTAL OR ABOUT \$6.8 BILLION. THE NATIONAL INSTITUTES OF HEALTH ALONE WILL PROVIDE \$4.8 BILLION, OR 70 PERCENT OF THE TOTAL FEDERAL INVESTMENT IN BIOMEDICAL RESEARCH. THE NIH IS RESPONSIBLE FOR OVER 35 PERCENT OF THE FUNDING FROM ALL SOURCES IN THE NATION.

DURING THE PAST DECADE THERE HAS BEEN A SIZEABLE INCREASE IN THE AMOUNT OF BIOMEDICAL RESEARCH SUPPORTED BY INDUSTRY. TEN YEARS AGO INDUSTRY'S EXPENDITURES IN THE UNITED STATES FOR HEALTH RESEARCH AND DEVELOPMENT AMOUNTED TO \$1.3 BILLION, OR ABOUT 27 PERCENT OF THE NATIONAL TOTAL. IN 1985, INDUSTRIES EXPECT TO SPEND ABOUT \$5 BILLION, OR 37 PERCENT OF THE NATIONAL TOTAL, AN AMOUNT SLIGHTLY MORE THAN THE SHARE SUPPORTED BY THE NIH. THAT, BY THE WAY, IS A CHANGE FOR UNTIL TWO YEARS AGO, NIH EXPENDITURES HAD EXCEEDED INDUSTRY'S TOTAL ANNUALLY SINCE WORLD WAR II. IN PART, THIS INCREASE IN INDUSTRIAL EXPENDITURES REFLECTS THE UPSURGE IN BIOTECHNOLOGY, FOR EXAMPLE, NEW INDUSTRIES EXPLOITING RECENT DEVELOPMENTS IN MOLECULAR BIOLOGY. IT IS WORTH NOTING THAT ALONG WITH INCREASED EXPENDITURES BY INDUSTRY, NEW KINDS OF RELATIONSHIPS HAVE BEEN ESTABLISHED BY INDUSTRIAL ORGANIZATIONS WITH SOME OF OUR FINEST ACADEMIC INSTITUTIONS. INGENIOUS CONTRACTUAL ARRANGEMENTS HAVE BEEN DEVELOPED TO PROTECT THE INTERESTS OF BOTH INDUSTRY AND ACADEMIA WITH SPECIAL ATTENTION TO SUCH ESSENTIALS AS FREEDOM OF INQUIRY AND OPEN SCIENTIFIC COMMUNICATION.

THERE IS MUCH TO BE GAINED BY ALL CONCERNED IN THESE NEW MODES OF COOPERATION. WHILE THE NIH HAS NOT INTERPOSED ITSELF INTO THESE JOINT ENTERPRISES, WE HAVE DEEP AND CONTINUING INTEREST IN THEM AND IN THEIR SUCCESS.

OUR AGENCY'S KEEN INTEREST IN THE STATUS OF INSTITUTIONS OF HIGHER LEARNING IS MORE THAN A GENERALIZED CONCERN FOR THE GOOD OF SCIENCE. NIH RESEARCH PROGRAMS ARE ROOTED DEEPLY IN ACADEMIC INSTITUTIONS, ESPECIALLY SCHOOLS OF MEDICINE. WITHIN THIS YEAR, MORE THAN 80 PERCENT OF THE TOTAL NIH BUDGET OF OVER \$5 BILLION WILL BE AWARDED TO ACADEMIC INSTITUTIONS, HOSPITALS, AND A VARIETY OF LABORATORIES FOR THE SUPPORT OF BIOMEDICAL RESEARCH. HALF OF THOSE AWARDS WILL BE MADE FOR THE SUPPORT OF RESEARCH CONDUCTED AT MEDICAL SCHOOLS.

AT THE NIH, OUR PRIME INSTRUMENT FOR THE SUPPORT OF BIOMEDICAL RESEARCH IS THE PROJECT GRANT AWARDED IN RESPONSE TO INVESTIGATOR-INITIATED PROPOSALS. IN MOST INSTANCES, THESE INVESTIGATORS ARE MEMBERS OF THE FACULTY OR AFFILIATED STAFF OF MEDICAL SCHOOLS. A LITTLE OVER HALF OF THE TOTAL NIH BUDGET, OR MORE THAN \$2.5 BILLION, IS EXPENDED FOR SUCH GRANTS. THROUGH THIS AND OTHER GRANT MECHANISMS, THE NIH CURRENTLY IS RESPONSIBLE FOR THE DEPLOYMENT OF ABOUT 50,000 NON-FEDERAL SCIENTISTS, AT LEAST PART TIME, AT MORE THAN 1,200 INSTITUTIONS IN PURSUIT OF PROJECTS INITIATED WITHIN THE SCIENTIFIC COMMUNITY. FURTHERMORE, THE NIH RECEIVES CRUCIALLY IMPORTANT ADVICE AS TO THE SCIENTIFIC MERIT OF INDIVIDUAL PROPOSALS THROUGH PEER REVIEW PROVIDED BY MORE THAN A HUNDRED PANELS OF NON-FEDERAL SCIENTISTS.



THE MECHANISMS EMPLOYED BY THE NIH HAVE SERVED WELL OUR GOAL OF SECURING THE MAXIMUM INVOLVEMENT OF OUR COUNTRY'S SCIENTIFIC COMMUNITY IN CREATIVE BIOMEDICAL RESEARCH. IN ONE AREA, HOWEVER, WE HAVE FOUND IT DIFFICULT TO FULFILL INCREASING RESEARCH NEEDS. THE NUMBER OF OPTIMALLY TRAINED PHYSICIAN-INVESTIGATORS HAS NOT KEPT PACE WITH THE FIELD. PHYSICIAN-INVESTIGATORS HAVE SPECIAL INSIGHTS TO OFFER, AND IN SOME INSTANCES THEY ARE ABSOLUTELY ESSENTIAL TO THE CONDUCT OF NEEDED RESEARCH STUDIES.

TO IDENTIFY SOME OF THE REASONS FOR THESE SHORTAGES, IT IS HELPFUL TO REVIEW SOME HISTORICAL CURRENTS IN SCIENCE AND MEDICINE.

IN THE PAST HALF CENTURY, A REVOLUTION HAS TAKEN PLACE IN BIOLOGY--A REVOLUTION SO SWEEPING IN ITS SCOPE AS TO TRANSFORM OUR UNDERSTANDING OF ALL LIVING THINGS. IN LITTLE MORE THAN A GENERATION, THE SCIENTIFIC COMMUNITY HAS WITNESSED THE DEVELOPMENT OF WHAT HAS BEEN CALLED "A COHERENT, IF PRELIMINARY, OUTLINE OF THE NATURE OF LIFE."<sup>1</sup>

THE EXPLOSION IN KNOWLEDGE HAS BROUGHT NEW VIGOR INTO PRACTICALLY EVERY BRANCH--EVERY DISCIPLINE--OF THE SCIENCE OF BIOLOGY AND AT THE SAME TIME HAS CREATED NEW BRANCHES. THE EXPANSION AND BRANCHING, SURPRISINGLY, HAVE NOT RESULTED IN THE FRAGMENTATION THAT ONE MIGHT EXPECT BUT RATHER HAS FOSTERED A KIND OF CONVERGENCE.

180

NOBEL LAUREATE ARTHUR KORNBERG PERCEIVED THIS PARADOX AND CAPTURED ITS SIGNIFICANCE IN A BRIEF PARAGRAPH. HE NOTED THE EXTRAORDINARY RECENT DEVELOPMENTS IN GENETIC CHEMISTRY AND IMMUNOLOGY BUT ASSERTED THAT "...THERE IS AN EVEN MORE PROFUND DEVELOPMENT IN MEDICAL SCIENCE, A CHANGE THAT IS TRULY REVOLUTIONARY AND YET ONE NEVER HEARS IT MENTIONED." THAT DEVELOPMENT, HE SAID, "...IS THE CONFLUENCE OF THE MANY DISCRETE AND PREVIOUSLY UNRELATED MEDICAL SCIENCE SUBJECTS INTO A SINGLE UNIFIED DISCIPLINE. ANATOMY, PHYSIOLOGY, BIOCHEMISTRY, MICROBIOLOGY, IMMUNOLOGY, AND GENETICS HAVE NOW BEEN MERGED AND ARE EXPRESSED IN A COMMON LANGUAGE OF CHEMISTRY." HE MAINTAINED THAT "BY REDUCING STRUCTURES AND SYSTEMS TO MOLECULAR FORMS, ALL ASPECTS OF BODY FORM AND FUNCTION BLEND INTO A LOGICAL FRAMEWORK."<sup>2</sup>

CONCURRENTLY WITH SUCH CONVERGENCE, HOWEVER, OUR PERSONNEL RESOURCES FOR CLINICAL INVESTIGATION HAVE BEEN WEAKENED BECAUSE THE CAREER TRACKS ENTERED BY STUDENTS IN MEDICAL SCHOOL SEEM TO DIVERGE. THE DIVISION DOES NOT OCCUR SO MUCH ALONG DISCIPLINARY LINES BUT MORE IN RESPONSE TO THE CIRCUMSTANCES THAT FORCE SOME OF OUR BRIGHTEST YOUNG MEN AND WOMEN TO MAKE SHARPLY DELINEATED "EITHER/OR" CHOICES--TO CHOOSE WHETHER TO PRACTICE MEDICINE OR TO CONDUCT RESEARCH.

NOT LONG AGO, IN SIMPLER TIMES, THE WELL-TRAINED PHYSICIAN WAS EXPECTED TO COMBINE RESEARCH WITH MEDICAL PRACTICE. PHYSICIANS WHO

APPLIED SCIENTIFIC TECHNIQUES TO THEIR OBSERVATIONS AND INVESTIGATIONS IN THE COURSE OF DIAGNOSIS AND TREATMENT WERE REWARDED WITH DIVIDENDS OF NEW MEDICAL KNOWLEDGE. THE WORKS OF THE GREAT PIONEERS, KOCH, PASTEUR, AND LISTER, WERE EXTENDED AND AMPLIFIED THROUGH THE EXPERIMENTS AND INSIGHTS OF SUCH INDIVIDUAL PHYSICIANS. DURING THE LAST THREE DECADES OF THE NINETEENTH CENTURY, YOUNG AMERICANS TRAINED IN MEDICAL CARE AND MEDICAL RESEARCH RETURNED HOME FROM EUROPE FILLED WITH ENTHUSIASM ABOUT THE PROGRESS MADE POSSIBLE BY THE FINDINGS OF THE GIANTS OF EUROPEAN SCIENCE. IT WAS DURING THIS PERIOD THAT MODEST BEGINNINGS WERE MADE IN ESTABLISHING LABORATORIES IN THE UNITED STATES DEDICATED TO BIOMEDICAL RESEARCH. ONE SUCH LABORATORY, A PART OF THE MARINE HOSPITAL SERVICE IN NEW YORK, MUCH LATER BECAME THE NATIONAL INSTITUTES OF HEALTH. WE WILL CELEBRATE OUR CENTENNIAL IN 1987.

EARLY IN THE TWENTIETH CENTURY, SEVERAL OF THE MAJOR MEDICAL SCHOOLS IN THE UNITED STATES BEGAN TO CHANGE THEIR ORIENTATION FROM EXCLUSIVE PREOCCUPATION WITH MEDICAL PRACTICE TO A STRONG AND ENTHUSIASTIC EMPHASIS ON RESEARCH, INCLUDING THE BASIC SCIENCES. DURING WORLD WAR II, OUR MEDICAL SCHOOLS PERFORMED DOUBLE DUTY IN SERVING THE NATIONAL INTEREST BOTH AS SOURCES OF NEEDED MEDICAL MANPOWER AND AS PRODUCTIVE BIOMEDICAL RESEARCH LABORATORIES. IN THE POSTWAR PERIOD, THE NATIONAL ENTHUSIASM FOR SUPPORTING MEDICALLY RELATED RESEARCH INTENSIFIED WHILE AT THE SAME TIME THE NUMBERS OF MEDICAL SCHOOLS INCREASED. RESEARCH WAS FULLY INTEGRATED INTO THE

PROGRAMS OF MOST SCHOOLS. BY 1960, FEDERAL SUPPORT FOR RESEARCH WAS THE LARGEST INCOME ITEM IN THE BUDGET OF MOST MEDICAL SCHOOLS IN THE UNITED STATES. IN THE PAST DECADE, INCOME FROM PATIENT CARE BY FACULTY MEMBERS HAS SURPASSED RESEARCH DOLLARS AS THE PRINCIPAL SOURCE OF FUNDING FOR THE OPERATIONS OF MEDICAL SCHOOLS, BUT THE CENTRAL IMPORTANCE OF RESEARCH TO THE MAINTENANCE AND ENHANCEMENT OF INSTITUTIONAL QUALITY IS FULLY APPRECIATED.

HOWEVER, FOR THE INDIVIDUAL MEN AND WOMEN AT VARIOUS STAGES IN THEIR TRAINING TO BE PHYSICIANS, THE DISTINCTION SEEMS TO BE MORE SHARPLY DRAWN THAN BEFORE BETWEEN RESEARCH AND THE PRACTICE OF MEDICINE. THIS DIVERGENCE DOES NOT BODE WELL FOR THE FUTURE OF RESEARCH NOR DOES IT AUGUR WELL FOR PATIENT CARE. DR. DAVID A. HAMBURG, FORMER PRESIDENT OF THE INSTITUTE OF MEDICINE OF THE NATIONAL ACADEMY OF SCIENCES, SOUNDED THE WARNING FIVE YEARS AGO THAT "WE MUST DO EVERY THING IN OUR POWER TO SEE THAT THE GREAT FUNDAMENTAL ADVANCES--INDEED THE INSPIRING ADVANCES IN MOLECULAR AND CELLULAR BIOLOGY--WILL BE AVAILABLE AS SOON AS POSSIBLE FOR HEALTH INTERVENTIONS OF A DEMONSTRABLY USEFUL CHARACTER. BUT THE AUTHENTIC BIOLOGICAL REVOLUTION THAT HAS BEEN GENERATED BY SEVERAL DECADES OF INTENSIVE BASIC RESEARCH IS NOT EASILY TRANSLATED INTO CLINICALLY VALID APPLICATIONS. AN INTERPRETER IS NEEDED AND IT IS THE CLINICAL INVESTIGATOR WHO SERVES THAT FUNCTION. THE FLOW OF INFORMATION IS BY NO MEANS UNIDIRECTIONAL; IF BASIC SCIENCE HAS SOMETHING TO SAY TO CLINICAL INVESTIGATION, SO TOO DOES CLINICAL INVESTIGATION OFFER



MUCH TO BASIC SCIENCE. CLINICAL RESEARCH REMAINS THE VITAL BRIDGE BETWEEN ADVANCES IN BASIC SCIENCE ON THE ONE HAND AND IMPROVEMENTS IN HEALTH CARE--DIAGNOSTIC, THERAPEUTIC, OR PREVENTIVE--ON THE OTHER."

DR. HAMBURG WENT ON TO SAY, "I WAS CONCERNED IN 1975 AND REMAIN CONCERNED TODAY THAT THE INTERWOVEN FABRIC OF BASIC SCIENCE AND CLINICAL INVESTIGATION IS TO SOME EXTENT UNRAVELING."<sup>3</sup> I SHARE DR. HAMBURG'S CONCERN. WE NEED TO LOOK AT A NUMBER OF FACTORS THAT APPEAR TO BE CONTRIBUTING TO A DECLINING INTEREST IN CLINICAL INVESTIGATION ON THE PART OF YOUNG PHYSICIANS.

THE ABSOLUTE NUMBER OF NIH TRADITIONAL RESEARCH GRANTS AWARDED TO M.D.S FELL FROM ABOUT 3,400 IN 1968 TO ABOUT 2,500 IN 1973. THERE HAS BEEN SOME RECOVERY SINCE, BUT THE NUMBER WAS STILL BELOW 3,000 IN 1983. NIH CURRENTLY FUNDS MORE THAN 16,000 INVESTIGATOR-INITIATED RESEARCH PROJECT GRANTS COMPARED WITH 9,000 IN 1972. BUT THE INCREMENT HAS GONE ALMOST ENTIRELY TO PH.D. APPLICANTS. ACCORDINGLY, THE PERCENTAGE OF NIH RESEARCH GRANTS HELD BY M.D.S HAS FALLEN PROGRESSIVELY OVER THE YEARS. IN THE 1960s, M.D.S HELD ABOUT 45 PERCENT OF ALL NIH GRANTS: CURRENTLY, M.D.S HOLD ONLY ABOUT 22 PERCENT.

THE DECLINE IN PERCENTAGE OF M.D. INVESTIGATORS WORKING UNDER PROJECT GRANTS REFLECTS IN PART THE SUBMISSION OF RELATIVELY FEWER

GRANT APPLICATIONS BY M.D.S. IN 1970, FOR EXAMPLE, M.D.S COMPRISED ABOUT 30 PERCENT OF THE APPLICANTS; BY 1980, ONLY 24 PERCENT. ANOTHER IMPORTANT FACTOR IS THE INTENSE COMPETITION. WHEN ONE LOOKS AT THE SUCCESS RATE OF NEW APPLICANTS ALONE, ONE FINDS THAT FOR THE PAST 15 YEARS NEW M.D. APPLICANTS HAVE COMPETED LESS WELL THAN NEW PH.D. APPLICANTS, WITH BOTH GROUPS COMPETING LESS SUCCESSFULLY THAN THE M.D./PH.D. APPLICANT.

THE SIMPLISTIC EXPLANATION THAT GREATER DIFFICULTY IS INHERENT IN WORKING WITH HUMAN SUBJECTS IS PROBABLY NOT THE ANSWER TO THE LOWER APPROVAL RATES FOR CLINICAL RESEARCH PROPOSED BY PHYSICIAN INVESTIGATORS. FOR AS WE KNOW, SCIENCE HAS BECOME COMPLEX, THE METHODS INTRICATE, AND THE TRAINING PERIODS SO LONG THAT THE PHYSICIAN, EVEN AFTER TWO OR THREE YEARS OF FELLOWSHIP TRAINING, REMAINS LESS WELL TRAINED THAN THE PH.D. SCIENTIST WHO HAS BEEN TRAINING FOR A RESEARCH CAREER SINCE THE BACCALAUREATE DEGREE. IN MY VIEW, THE TRENDS OF THE PAST TWO DECADES REFLECT THE PROGRESSIVE PROFESSIONALIZATION OF BIOMEDICAL RESEARCH, IN PARTICULAR OF CLINICAL RESEARCH. I HOPE THERE WILL ALWAYS BE ROOM FOR THE CREATIVE AMATEUR IN CLINICAL INVESTIGATION, BUT HISTORY INDICATES THAT SUCH A PERSON IS LESS LIKELY TO SECURE EXTERNAL SUPPORT FOR HIS OR HER WORK. SUCCESS FOR AN M.D. INVESTIGATOR IS INCREASINGLY DEPENDENT UPON SUBSTANTIAL TRAINING IN THE INFORMATION CONCEPTS AND METHODOLOGIES OF COMPLEX MODERN SCIENCE. TO BE A FIRST-RATE SCIENTIST AND A WELL-QUALIFIED PHYSICIAN IS A DEMANDING CALLING.

PROGRAMS HAVE BEEN LAUNCHED IN OUR COUNTRY BY THE GOVERNMENT, BY INDUSTRY, BY VOLUNTARY HEALTH ORGANIZATIONS, AND BY PHILANTHROPIC FOUNDATIONS FOR THE PURPOSE OF INCREASING THE NUMBER OF WELL-TRAINED CLINICAL INVESTIGATORS. SEVERAL OF THESE INITIATIVES ARE BASED ON THE OBSERVATION THAT MOST MEDICAL SCHOOLS CURRICULA PROVIDE LITTLE OR NO LABORATORY EXPERIENCE THAT IS REPRESENTATIVE OF MODERN DAY MEDICAL SCIENCE. THE RISE OF SPECIALTY FIELDS AND THE LENGTHENING OF POSTDOCTORAL TRAINING PROGRAMS HAVE EXTENDED THE CLINICAL TRAINING NECESSARY FOR BOARD CERTIFICATION. THE REQUIREMENTS OF MANY CERTIFICATION BOARDS ARE TO A CONSIDERABLE DEGREE INFLEXIBLE AND DO NOT ENCOURAGE THE POTENTIALLY CREATIVE PHYSICIAN TO ENTER RESEARCH TRAINING.

AT THE UNDERGRADUATE MEDICAL SCHOOL LEVEL, THE NIH GIVES ITS MEDICAL SCIENTIST TRAINING PROGRAM (MSTP) TOP PRIORITY IN OUR TRAINING PORTFOLIO. THIS PROGRAM IS SUPPORTED AT A LIMITED NUMBER OF INSTITUTIONS THAT HAVE A HISTORY OF HIGH ACADEMIC PERFORMANCE AND RESEARCH PRODUCTIVITY TO TRAIN INDIVIDUALS FOR BOTH THE M.D. AND THE PH.D. DEGREE. SEVENTY PERCENT OF THE GRADUATES OF THIS SIX-YEAR PROGRAM HOLD POSITIONS IN MEDICAL SCHOOLS, PERFORMING RESEARCH, AND ENGAGING IN THE TRAINING OF STUDENTS AND OTHER PHYSICIANS. WE CURRENTLY ARE SUPPORTING 682 STUDENTS AT 25 INSTITUTIONS UNDER THIS PROGRAM. THE NIH ALSO HAS A NUMBER OF PROGRAMS THAT PROVIDE SUPPORT FOR EARLY STUDENT EXPOSURE TO RESEARCH CAREERS DURING THE SUMMER MONTHS OR IN OFF QUARTERS.

AN INNOVATIVE ADDITION TO NIH PROGRAM RESOURCES IS THE JOINT NIH-HOWARD HUGHES MEDICAL INSTITUTE SCHOLARS PROGRAM. IN THIS ACTIVITY, WHOSE PURPOSE IS TO ATTRACT MEDICAL STUDENTS INTO RESEARCH, THE HOWARD HUGHES MEDICAL INSTITUTE WILL SUPPORT THE RESEARCH TRAINING OF 25 TO 30 MEDICAL STUDENTS AT NIH FOR FROM NINE MONTHS TO A YEAR FOLLOWING THEIR SECOND YEAR IN MEDICAL SCHOOL. THE JOINT AGREEMENT PROVIDES FOR FUNDING BY THE HUGHES INSTITUTE FOR STIPENDS AND TRAVEL EXPENSES FOR THE TRAINEES WHO WILL PARTICIPATE IN RESEARCH ACTIVITIES IN OUR INTRAMURAL LABORATORIES, SIDE BY SIDE WITH SOME OF NIH'S LEADING SCIENTISTS. THE HUGHES FUNDING WILL ALSO MAKE POSSIBLE A STRUCTURE ON THE NIH CAMPUS FOR LIVING QUARTERS, CLASSROOMS, AND TEACHING LABORATORIES. THE FIRST CLASS OF 25 STUDENTS, SELECTED IN NATIONWIDE COMPETITION, HAS JUST ENTERED TRAINING AT NIH.

OTHER OF OUR TRAINING PROGRAMS ARE INTENDED FOR PHYSICIANS WHO HAVE COMPLETED MEDICAL SCHOOL AND SEVERAL YEARS OF CLINICAL TRAINING WITHOUT ANY SPECIAL RESEARCH EXPERIENCE. MOST SUCH PHYSICIANS ARE UNPREPARED FOR RESEARCH. EVEN WHERE THEY MIGHT HAVE PARTICIPATED SUCCESSFULLY IN ONE OR MORE RESEARCH PROJECTS, THE EXPERIENCE DOES NOT SUBSTITUTE FOR A PLANNED PROGRAM TO DEVELOP RESEARCH EXPERTISE. A SERIES OF NIH AWARDS, CALLED RESEARCH CAREER DEVELOPMENT AWARDS (RCDA), HAS BEEN DEVELOPED FOR PHYSICIANS IN THIS SITUATION. THE OLDEST OF THESE IS THE AWARD SOLELY FOR SALARY AND FRINGE BENEFITS. MORE THAN 80 PERCENT OF THOSE WHO RECEIVED RCDAS IN THE PAST NOW ARE



RECEIVING SUPPORT FROM A RESEARCH PROJECT GRANT. SIMILAR AWARDS INCLUDE AN ACADEMIC INVESTIGATOR AWARD, THE CLINICAL INVESTIGATOR AWARD, THE MID-CAREER DEVELOPMENT AWARD, AND THE PHYSICIAN-SCIENTIST AWARD. THESE PROVIDE A SALARY WITH FINANCIAL BENEFIT SUPPORT AND SOME LABORATORY SUPPORT FOR PERIODS OF 3-5 YEARS OF TRAINING, NOT SERIOUSLY DILUTED BY CLINICAL DUTIES AND THE AMBIGUOUS GOALS OF SUBSPECIALTY TRAINING. OFTEN THESE PROGRAMS OFFER SEVERAL YEARS OF BASIC SCIENCE EXPERIENCE BEFORE ENTERING CLINICAL RESEARCH.

A NUMBER OF FOUNDATIONS, INDUSTRIAL ORGANIZATIONS, AND VOLUNTARY HEALTH AGENCIES HAVE DEVELOPED FELLOWSHIP PROGRAMS AND AWARDS FOR PHYSICIANS, ENCOURAGING OR ASSISTING THEM IN CAREERS OF CLINICAL RESEARCH. SUCH AWARDS USUALLY SPECIFY THAT 90-100 PERCENT OF THE SUPPORTED TIME BE DEVOTED TO RESEARCH. THESE PHYSICIANS WILL PURSUE INDEPENDENT PROJECTS IN U.S. MEDICAL SCHOOLS, WITH THEIR STUDIES FOCUSED ON SUCH SUBJECTS AS INFECTIOUS DISEASES, CARDIOVASCULAR MEDICINE, DIABETES, RHEUMATOLOGY, AND BIOLOGICAL PSYCHIATRY.

ALL OF THESE EFFORTS ARE CONSTRUCTIVE AND WE BELIEVE WILL BE EFFECTIVE IN INCREASING THE ESSENTIAL PARTICIPATION BY PHYSICIANS IN BIOMEDICAL RESEARCH. AND SUCH PARTICIPATION YIELDS MULTIPLE BENEFITS, FOR IN MEDICINE, BIOMEDICAL RESEARCH, TEACHING AND PATIENT CARE ARE MUTUALLY REINFORCING ACTIVITIES.

THIS TRUTH IS ELOQUENTLY EXPRESSED IN A QUOTATION CARVED IN THE MARBLE WALL AT THE ENTRANCE TO THE AUDITORIUM OF THE NIH CLINICAL CENTER. THE QUOTATION IS FROM THE CENTER'S FIRST DIRECTOR, DR. JACK MASUR, FOR WHOM THE AUDITORIUM IS NAMED. IT READS, "HOSPITALS WITH LONG TRADITIONS OF EXCELLENCE HAVE DEMONSTRATED ABUNDANTLY THAT RESEARCH ENHANCES THE VITALITY OF TEACHING; TEACHING LIFTS THE STANDARDS OF SERVICE; AND SERVICE OPENS NEW AVENUES OF INVESTIGATION."

# # #

#### REFERENCES

<sup>1</sup>HORACE FREELAND JUDSON, "THE EIGHTH DAY OF CREATION," P.10. *near 1977*

<sup>2</sup>KORNBERG UNPUBLISHED PAPER TITLED, "BIOLOGY AND TECHNOLOGY," APRIL 13, 1982, P.6. *author Kornberg*

<sup>3</sup>CONFERENCE SUMMARY, "CLINICAL INVESTIGATIONS IN THE 1980s-- NEEDS AND OPPORTUNITIES," INSTITUTE OF MEDICINE, NATIONAL ACADEMY PRESS, P.2. *1981 author-year*

*514-544-145  
Ext 233*

*Dr. Nicholas P. ...*

*Chair ...*



STATEMENT OF

JAMES B. WYNGAARDEN, M.D.

DIRECTOR

NATIONAL INSTITUTES OF HEALTH

PUBLIC HEALTH SERVICE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON LABOR-HHS-EDUCATION

COMMITTEE ON APPROPRIATIONS

U.S. SENATE

SEPTEMBER 26, 1985

FOR RELEASE UPON DELIVERY ONLY



Mr. Chairman:

I am pleased to provide the Committee with an overview of ongoing activities and research objectives of the National Institutes of Health (NIH) on Acquired Immunodeficiency Syndrome (AIDS). Although tremendous progress has been made, much remains to be learned concerning the treatment of AIDS patients and the ultimate prevention of this deadly disease.

AIDS continues to be recognized by Secretary Heckler as the number one public health priority of the Department of Health and Human Services (HHS). With the support and leadership of the Secretary, the Administration, and the Congress, NIH has maintained a strong and growing research effort prior to and since the first AIDS patients were admitted to the NIH Clinical Center more than four years ago. We are committed to determining the frequency and distribution of AIDS in the population, its mode of transmission, and the means for treatment and prevention of the disease.

Although the problem of AIDS is far from solved, research carried out by NIH grantees, and at the NIH itself during these years, has led to a dramatic accumulation of information about various aspects of the disease. Certainly, tremendous impetus for the AIDS research program was provided by the clear delineation by scientists in the National Cancer Institute (NCI) early in 1984, that a retrovirus, human T-cell lymphotropic virus type III (HTLV-III), is the underlying cause of AIDS. This discovery led to changes in direction in many research studies, opened new opportunities for research on treatment of patients and on prevention strategies, presented new avenues for development of vaccines, and resulted in a blood screening test to reduce transmission through transfusion.

We recognize that AIDS research and its associated planning must be a dynamic process, punctuated by new discoveries and the inevitable adjustments that these developments impose. The NIH planning and budget processes allow the flexibility needed to redirect our focus and best utilize our resources. To assure that NIH would be prepared to respond rapidly and be fully informed of all AIDS activities, the NIH Working Group on AIDS was established in 1982 to coordinate and exchange information among the Bureaus, Institutes, and Divisions of NIH, as well as with the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), the Centers for Disease Control (CDC) and the Food and Drug Administration (FDA). This high level of collaboration was enhanced by the creation by the Assistant Secretary for Health of the PHS AIDS Executive Task Force to expedite the large-scale practical applications of AIDS and AIDS-related findings. The NIH working group was replaced by the NIH AIDS Executive Committee, which was established in June 1984. The purpose of the NIH AIDS Executive Committee is to keep the NIH Director fully informed on AIDS and AIDS-related matters. The committee also provides a mechanism to heighten coordination among elements of the NIH so that all new research opportunities are fully exploited. As the need arises, the NIH AIDS Executive Committee establishes subcommittees to address specific problems, such as the subcommittee for the development and testing of prophylactic and therapeutic modalities for the control of AIDS and the subcommittee for the development of appropriate animal models.

#### CURRENT DIRECTIONS

Research supported and conducted by NIH includes studies of the chemistry and biology of the causative virus itself; basic studies supporting the

development of reliable diagnostic tests for AIDS; epidemiologic studies, including examination of cofactors that might play a role along with HTLV-III in causing AIDS; work aimed at reconstituting the immune system in AIDS patients; inhibiting and eradicating the retrovirus (HTLV-III) with antiviral agents and controlling the opportunistic infections and cancers characteristic of the disease; application of several techniques to the development of vaccines, including the search for animal models for AIDS; and studies aimed at more effective screening of donated blood.

Special emphasis is being given to drug research and testing in the treatment of AIDS. With the discovery of the causative agent, scientists now know that research on treatment modalities must be simultaneously focused on developing antiviral agents to inhibit the replication of the virus, reconstituting the immune system, and treating the opportunistic infections that afflict AIDS patients. It is likely that the patients will have to be treated with at least two agents simultaneously, an antiviral agent and an immune enhancer, in order to successfully combat the disease. However, more research is needed to answer this point definitively. Antiviral agents identified as having clinical potential are currently being tested or are in preparation for testing. Studies must first be done to ensure that these drugs are generally safe, and will not further compromise the weakened state of the patient with AIDS.

In regard to vaccine development, NIH researchers working in close cooperation with colleagues at the FDA are currently investigating a number of preparations made by breaking up the whole AIDS virus and extracting

antigens. These preparations are now being tested in animals for evaluation of their effectiveness as a potential vaccine. Additionally, a number of NIH investigators are using recombinant DNA technology in an attempt to clone appropriate gene segments of HTLV-III.

## RESEARCH OBJECTIVES

The NIH will capitalize on the extensive research on AIDS-related disorders, principally through epidemiologic studies to clarify the natural history of the disease and through additional work toward the development of vaccines and antiviral agents. Basic research will continue. Specific activities proposed for FY 1986 will include the following:

### Basic Research

The rapid progress that has been made thus far in AIDS research is due in large part to the extensive and farsighted previous investments in basic science, particularly in the areas of immunology and virology. Of course there is still much to be learned about the virology and pathogenicity of the virus. Therefore, the Institutes will continue to actively support basic research involving antigenic viral components, stressing antigens that are common to many virus strains and would elicit neutralizing and/or protective antibodies; latency; incorporation of the viral genome in the host cell and activating factors; inhibition of viral growth; isolation of the virus from various body fluids; identification of markers for predicting occurrence of



clinical disease in virus-exposed individuals; development of diagnostic tests and viral isolation; and the determination of genetic and other variations among HTLV-III isolates.

### Epidemiologic Studies

A wide range of epidemiologic research on AIDS is being conducted at NIH, by its grantees and in collaboration with other agencies of the PHS. The objectives of these studies are to develop an understanding of how infection occurs, how frequently and under what circumstances HTLV-III infection persists in infected individuals, and which infected individuals are most likely to transmit HTLV-III; the severity of disease in relation to time and source of infection; risk factors; time frames for the development of antibodies to HTLV-III; and the role of host factors and cofactors in disease risk. Examples include:

- o Studies in various populations to assess the prevalence of HTLV-III infection by using the HTLV-III antibody ELISA test and viral isolation. Groups to be examined include: Homosexual men, hemophiliacs, drug users, family contacts, hospital and laboratory personnel, blood donors, and several populations in the United States and in Haiti, Central Africa, and the Far East.
- o The National Institute of Allergy and Infectious Diseases (NIAID) support of a large multi-center study of the natural history of AIDS in homosexual men. Specifically, 5,000 homosexual men in Baltimore, San Francisco, Chicago, Los Angeles, and Pittsburgh are being followed

longitudinally for three years. The objective is to resolve issues concerning the clinical spectrum of HTLV-III infections, the implications of a positive serologic test for an individual, the prevalence of circulating and/or shed virus in antibody-positive persons, and the prognosis for seropositive individuals with mild or no signs of disease. A similar group of men from New York will be evaluated. While this study was originally set up to collect specimens in an attempt to determine the etiologic agent, it has been converted into a natural history study similar to the multicenter study. Biological specimens collected from each of these populations will be made available to intramural and extramural scientists for study.

- o A large study of the natural history of HTLV-III infection in newborn children. This involves the identification of HTLV-III positive pregnant women, spouses of patients, parenteral drug users, and Haitians, and the subsequent laboratory and clinical evaluation of their offspring up to two years of age.
- o Study and treatment of AIDS-associated ocular infections. Our investigators have demonstrated the presence of HTLV-III in human tears. Although it has not been shown that AIDS is transmissible through tears, this work points to the need to sterilize ophthalmic instruments that come in contact with the eye. Future work will examine the significance of HTLV-III in ocular fluids.

- o A large study of AIDS in Zaire through cooperative efforts of the NIAID, CDC, the Zairian Ministry of Health, and the Belgian Institute for Tropical Medicine. Special attention is being paid to the role of heterosexual contact and transmission within family units.
- o Followup studies of documented regional differences in the prevalence and exact nature of HTLV-III antibody in Kenya. The purpose is to clarify the basis for low AIDS case rates in areas endemic for HTLV-III.
- o Expansion of projects related to the high rates of viral isolation in seronegative sexual contacts of high-risk group members.
- o A study of HTLV-III transmission in seropositive, pregnant, drug-using females and their offspring, with followup of the children to monitor seroconversion, immune function, and risk of AIDS.
- o Interviews of persons occupationally exposed to HTLV-III regarding known AIDS risk factors and details of exposures (particularly needle-stick injuries) and serial collection of blood samples.
- o A followup of a drug-user cohort study which indicates striking geographic differences in seropositivity to assess changes in seroprevalence over time and the risk of AIDS and AIDS-related illnesses.

- o Evaluation of immune function of individuals at high risk for AIDS for at least two years to determine whether any of them develop AIDS symptoms. Attempts will be made to identify immune abnormalities that may be predictive for AIDS and could help elucidate the mechanisms leading to disease.
- o Studies to determine the role of agents as cofactors and their role in disease pathogenesis.
- o A study with clinical centers in New York, San Francisco, Miami, Los Angeles, Detroit, and Seattle to determine the incidence and natural history of HTLV-III infection. The study will include 1,000 hemophiliacs, 100 persons with sickle-cell disease, and about 150 with Cooley's anemia. Family members, sexual partners, and persons with the same disease who are less frequently transfused will be among the control population in this study. The results of the study will be important to understanding the role and relative risk of various types of blood components in transmission of HTLV-III.
- o Collection of serum samples from randomly selected volunteer blood donors at major blood centers in New York, San Francisco, Miami, and Los Angeles prior to the development of the HTLV-III test. This serum repository will be used for testing antibodies to HTLV-III, identification of seropositive donors and recipients of blood products from these donors, followup of the recipients, and data analysis.



This project also involves the study of the natural history of alterations in immune system function in heavily transfused patients and the relation of these alterations to the clinical development of AIDS.

- o Further studies related to AIDS encephalopathy and the substantial data that the retrovirus HTLV-III is present in the brain of AIDS patients. It is of clinical, therapeutic, and epidemiological importance to determine what percentage of currently seropositive individuals may harbor HTLV-III in their brains.
- o Investigation of the role of protein components of saliva that serve as a natural defense mechanism against Candida albicans, an opportunistic infection. There appears to be a definite association between AIDS and the presence of Candida albicans. The successful development of an assay for the antifungal proteins in saliva may help identify those at high risk of developing AIDS.

### Treatment

The objective of studies related to treatment is the development and evaluation of antivirals and immune stimulants, as well as combinations of these which are effective against AIDS. Research objectives being pursued in close collaboration with FDA in this critical area will include:

- o Immediate investigation of the efficacy and safety of HPA-23, made possible by the recent review of an investigational new drug (IND) application by the FDA.
- o Determination of whether a proposed therapy is effective. One highly sensitive indicator of the effectiveness of systemic treatment of AIDS is the persistence or disappearance of the ocular signs associated with cytomegalovirus retinitis in the 30 to 40 percent of AIDS patients estimated to have this opportunistic eye infection.
- o Methodologies for the control of opportunistic infections, such as evaluating the effectiveness of the antiviral drug 9-(1,3 dihydroxy-2-propoxymethyl) guanine (DHPG) in cytomegalovirus retinitis and colitis viral infections, often present in AIDS patients.
- o Phase I studies (that is, human subject studies designed to establish tolerable toxicities and monitor for pharmacological effects over a range of doses) of antivirals and immune modulators, which are being done in our intramural programs. Some of these studies involve interleukin-2, Ribavirin, Foscarnet, and Suramin. Agents having a tolerable toxicity level at dosages that show some stimulation of the immune system or are active against the AIDS virus will then move on to Phase II studies. (Phase II studies are basically an extension of Phase I studies, involving larger numbers of patients, to determine the effective dosages.) If these studies are successful, controlled efficacy trials, Phase III studies, will follow.

Of the agents under review, Suramin continues to be viewed as a promising drug, as there is strong evidence that it has clinical activity against HTLV-III. To date, a number of patients are involved in trials with this drug, and more trials are planned with larger numbers of patients. NIH continues to support these trials, which are performed both intramurally and at a number of institutions receiving extramural support.

- o Studies involving a large group of patients who are symptom-free high-risk subjects, subjects with AIDS-related complex (ARC), or subjects with AIDS. Investigators have defined the immunologic abnormalities in AIDS, and the plan is now to apply this information to the development of therapeutic approaches using immunorestorative agents.
- o Use of bone marrow transplants in an attempt to restore the immune system. Such transplants have been performed in two pairs of identical twins. Experience with this study showed there was some improvement in immune function, although one patient subsequently died. However, at that time the causative agent had not been identified, and efforts were directed at restoration of the immune system alone. We now know that combined therapy is indicated, because unless the virus itself is blocked, the immune system will deteriorate in the same way as the initial immune system did. Currently, three

pairs of identical twins are being studied. Suramin is being combined with bone marrow transplantation in the three patients with AIDS. It is too early to predict the results of these efforts.

- o Clinical trials with Ribavirin in the treatment of pediatric AIDS. Additional agents which have been effective in the treatment of animal retrovirus infections will be tested in chimpanzee HTLV-III models and in the Rhesus monkey AIDS model. In Phase I, promising antiviral agents will be tested for their efficacy in eliminating viremia. Serum and cerebrospinal fluid (CSF) levels of virus will be evaluated against dosage and toxicity. The animal model further allows testing of drug efficacy in clearing brain infections (as shown by selective serial brain biopsies) and assessment of antiviral efficacy and toxicity in pregnant and newborn HTLV-III infected animals.

### Prevention

NIH is working closely with agencies throughout the PHS in developing improved methods for detection and control of this disease. The principal objective of NIH efforts in the prevention area is to develop and evaluate better approaches for detecting infection as well as to develop passive and active immuno-prophylaxis. Broad-scale prevention and control activities emphasizing educational and information exchange must begin, in the absence of a vaccine and specific therapy. They should be based on current best public health judgment. A variety of activities will be undertaken in the prevention area including:



- o Improved methodology to detect AIDS antibody.
- o Attempts to develop methodologies for early detection of disease.
- o Simple, rapid, and sensitive methods for the detection and isolation of HTLV-III.
- o A great many methods of vaccine production will be considered. These will include extracting candidate antigens from large-scale production of virus, identifying appropriate antigens and synthesizing them, insertion of appropriate genomes in bacteria or yeast for antigen production, insertion of appropriate HTLV-III genome segments into vector viruses, and synthesis of peptides of the viral envelope products.
- o When candidate vaccine materials have been shown safe and antigenic in animals, Phase I clinical studies will begin in humans.
- o Hyperimmune serum and monoclonal antibodies will be developed to determine their feasibility in treatment of AIDS and/or ARC.

### Animal Models

The objective of these studies is to continue to develop animal models of AIDS in which candidate vaccines and drugs can be tested.

- o Studies of naturally occurring animal retrovirus infections simulating AIDS, such as Simian AIDS.
- o Studies on the transmission of HTLV-III from humans to nonhuman primates. These projects will attempt to establish a reproducible means to induce clinical manifestations of AIDS in nonhuman primates, in order to develop a better animal model for the disease. Such a model promises to provide investigators with means to assess the natural history of AIDS and evaluate a variety of interventive measures for the treatment or prophylaxis of human AIDS. Another aspect of these studies will be to mate infected or seropositive animals and study their offspring to further investigate maternal-fetal transmission of HTLV-III. Additionally, serial passage of HTLV-III will be made in chimpanzees, paralleling comparable studies of natural infections in man, to determine if antigenic drift occurs, an important factor in vaccine development.

### Outreach

Information programs have been designed to promote a fuller understanding of AIDS and to disseminate the latest research advances to those involved in the care of AIDS patients. For example:

- o A series of workshops, seminars, conferences, and outreach education programs aimed at different populations, including physicians, health

care workers, allied service personnel dealing with AIDS patients, and lay individuals. As an example, NIAID has developed an outreach education program specifically designed for health workers and allied support personnel who care for AIDS patients. These conferences have been held in a number of U.S. cities, and the program will continue. The purpose of the conferences is to provide the most recent information and to dispel myths and fallacies regarding AIDS. One of the major thrusts of this effort is discussion of the known facts and fallacies associated with modes of transmission and protection, and the currently accepted guidelines for the proper management of patients with AIDS. NIAID also plans to develop workshops on AIDS for presentation at national professional and lay organization meetings.

- o Current support by National Heart, Lung and Blood Institute to identify the most effective methods to inform and counsel blood donors who are identified as HTLV-III antibody positive will continue. Future activities in this area may include consensus development conferences on appropriate methods to counsel blood transfusion recipients, hemophiliacs, persons with sickle-cell disease or Cooley's anemia, and bone marrow recipients regarding their health status and lifestyle after exposure to HTLV-III.
- o Use of the Physician's Data Query (PDQ) system developed by NCI as a means of providing physicians with information about standard and experimental treatment of cancer, locations of experimental treatment, and the names of cancer specialists. To respond to the AIDS crisis

and make the most recent information on AIDS available to health practitioners, NCI has included information on ongoing AIDS studies in the PDQ system.

- o Provision of information support by the National Library of Medicine (NLM) through bibliographic and reference services. NLM is producing a comprehensive bibliography on AIDS, which will be available both to the Department and to extramural AIDS investigators.

#### Summary

Mr. Chairman, I believe I have provided the Committee with an overview of NIH activities that demonstrate our major commitment toward developing treatments, a vaccine, and ultimately a cure for AIDS. The fast pace of AIDS research at NIH and in the numerous research institutions in this country and around the world, makes almost any research planning effort dated before it is complete. NIH research efforts directed toward the AIDS problem are both logical and comprehensive. Our efforts, fully coordinated with other agencies of the PHS, are broad and multifaceted, since no one can predict which approach will ultimately be successful. We all hope for new findings in this area, and are prepared to apply those results to our research effort upon discovery.

This concludes my prepared statement. I will be pleased to answer any questions you may have.





REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

Today's ceremony marks two significant events. It could be called the public inauguration of the Research Scholars Program jointly established by the Howard Hughes Medical Institute and the National Institutes of Health. The founding class of Scholars, selected in June, have now begun their respective special training programs in the laboratories and at the side of some of our leading investigators.

The other event to be observed is the groundbreaking symbolizing the construction of a residence for the Research Scholars and renovation of the convent building. Upon completion, the Cloister will not only symbolize the private-public collaboration of which it is the product -- it will constitute a uniquely valuable resource in carrying out the high purposes of increasing the vitality of American biomedical research by enlarging the pool from which future physician researchers can be drawn. It was initially proposed by Dr. Donald Fredrickson. We salute you, Don, for your leadership at NIH, and now at HHMI. I would like to mention that Don is included among the 20 men and women who have had the greatest impact on the way we live in

---

\* At the Groundbreaking Ceremony for The Cloister at the Mary Woodard Lasker Center for the HHMI-NIH Scholars Program, October 1, 1985.

\*\* Director, National Institutes of Health, Bethesda, Maryland.

Washington, D.C., as cited in the Special 20th Anniversary Issue of The Washingtonian.

The remarkable HHMI-NIH collaborative program was launched in an unusually short time for a major undertaking of a federal agency. It could happen because officials at higher levels, particularly the then Assistant Secretary for Health Edward Brandt and Secretary Margaret Heckler, were quick to see the merit of the plan -- and to act constructively on its behalf.

Shortly after our formal recommendation was sent to Dr. Brandt and then to the Secretary, we received word that she was enthusiastic about it -- and she acted accordingly.

Madam Secretary, we are very pleased that you are with us today. You have shown your deep interest in many programs of the NIH and it has been our pleasure to have your public participation in a number of special events here. On many other occasions you have shown your understanding and strong support of our activities.

I am especially pleased and honored to present Margaret Heckler, the Secretary of Health and Human Services.

Secretary Heckler . . .

It is an honor and a pleasure to introduce Congressman William H. Natcher of Bowling Green, Kentucky. Since his election to the House in 1953, he has never missed a vote -- an all-time record. Mr. Natcher has been Chairman of the Appropriations Subcommittee on Labor, Health and Human Services, and Education since 1979. Throughout his tenure in the House he has shown

himself to be a staunch supporter of the NIH and of health research in general.

It is through the efforts of the health subcommittee chaired by Mr. Natcher that NIH was able to acquire the convent grounds for the Lasker Center, which in turn has permitted the establishment of the HHMI-NIH Research Scholars Program. Without men of vision like Congressman Natcher, this celebration would never have occurred.

Thank you and welcome, Mr. Congressman . . .





## FUNDING OF BIOLOGICAL RESEARCH\*

by

James B. Wyngaarden, M.D.\*\*

In discussing the "Funding of Biological Research," I will direct my remarks largely to a sketch of organizational aspects of the biomedical science establishment in the United States and to comments on the trends in funding for research by the Federal Government, by industry, and by other interests.

Our most recent projection of total expenditures for health research and development in this country during 1985 is about \$13.5 billion. The Federal Government is expected to be the source of just over one-half of the total or about \$6.8 billion. The National Institutes of Health (NIH) alone will provide about \$4.8 billion or 70 percent of the total Federal investment in biomedical research. The NIH is responsible for over 35 percent of the funding from all sources in the nation.

During the past decade there has been a sizeable increase in the amount of biomedical research supported by industry. Ten years ago, industry's expenditures in the United States for health research and development amounted to \$1.3 billion or about 27 percent of the national total. In 1985, industries expect to spend about \$5 billion or 37 percent of the national total, an amount slightly more than the share supported by the NIH. That, by the way, is a change for until two years ago, NIH expenditures had exceeded industry's total annually since World War II. In part this increase in industrial expenditures reflects the upsurge in biotechnology, for example, new industries exploiting recent developments in biotechnology. It is worth noting that along with increased expenditures by industry, new kinds of relationships have been established by industrial organizations with some of our finest academic institutions. Ingenious contractual arrangements have been developed to protect the interests of

---

\*Address given at Seminar on Biology,  
Yale University, New Haven, CT, October 2, 1985.

\*\*Director, National Institutes of Health, Bethesda, MD

In the past decade, we have become increasingly concerned about maintaining a relatively stable and predictable level of new and competing renewal project grants. The number of competing awards has fluctuated greatly since 1970, ranging from a total of 2,580 in FY 70 to a high of 5,944 in 1979. Such fluctuations not only create financial problems for grantee institutions but adversely influence the career decisions of graduate students as well as young scientists. (Slide 3)

We have recognized that to assure future health gains, the current national research capability must be sustained and enhanced. As applied to research project grants, a major goal was to minimize the year-to-year fluctuations in the number of competing grants. The goal of funding at least 5,000 new and competing renewal grants atop a base of moral commitments of 11,000 continuation grants was considered a major feature of the "stabilization" policy. While we have indeed supported at least 5,000 competing research project grants each year since 1980, budgetary limitations have precluded a comparable degree of stability for other research and training programs of the NIH. (Slide 4)

#### Increased Competition and Some of Its Effects

The marked increase in the number of meritorious applications for grants characteristic of the past decade has outstripped the availability of resources and intensified competition. In 1975 we were able to fund about 60 percent of grants eligible for award, but in 1984 the award rate was about 37 percent. (Slide 5) From the NIH perspective, the approved but unfunded grants constitute an index of the scientific opportunities that we currently are unable to pursue. From the viewpoint of the applicant, these figures mean that an increasing number of investigators whose research careers often depend upon successful competition for grant support are failing to obtain that support.

A measure that is perhaps more meaningful to the applicant is the success rate--that is, the ratio of the number of awards to the number of applications reviewed. In 1975 the success rate was 45 percent. In 1984 it was 32 percent. (Slide 5)



Another complication from increased competition that arises in the peer review system is the steadily better level of priority scores being assigned by reviewers. This trend appears to reflect both improvements in quality of research proposals and perhaps "grade creep." Scores increasingly are compressed, shifting the average NIH paylines from 255 in 1975 to 190 in 1984.

Furthermore, grant proposals are increasingly being resubmitted after unsuccessful competitive review. In 1965, 6 percent of applications reviewed were resubmissions. In 1975, the ratio was 15 percent, and during 1985, we estimate the proportion of resubmissions will be 25 percent.

Resubmitted applications in essence are proposals amended to remedy deficiencies identified in the review process, for the unsuccessful investigators endeavor to meet the criticisms spelled out in the Summary Statements. As might be expected, resubmitted applications enjoy a higher success rate than proposals submitted de novo. But there are several undesirable effects of the growing number of resubmitted grant applications. The first is a decrease in the efficiency of the peer review system for both applicant and reviewer. An increased number of applications must now be prepared and reviewed two or more times before a decision is reached. There is also the repetition of the work of processing for the Division of Research Grants. All of this translates into a substantial increase of cost in time (and dollars) per award made. The second undesirable effect is that of escalation of length and complexity of applications. Much of this is a reflection of the rising level of competition resulting from the decline in award and success rates. This factor has prompted applicants to expand the details of documentation of every aspect of the proposal in order to gain a competitive edge. A resubmitted application is likely to carry this trend to an even further extreme in answer to study section criticisms. This results in further escalation of the work per application for all concerned. But even this factor, important as it is, is not the worst of the undesirable effects.



My view is that in sum this progressive and continuing shift toward increasing specification of all details of the application has resulted in an unintended but fundamental alteration of the philosophy of award itself from that of investment to that of procurement. In an effort to discriminate among excellent proposals, study sections have sought for reasons to assign less competitive priority scores or to recommend only the minimal number of years necessary to accomplish the precise goals of the study. The result is that applications tend toward contract documents in form and substance. There is a sense, difficult to prove, that safe proposals, often with substantial portions of the research accomplished prior to submission of the application, predominate, and that more creative, higher risk research applications are discouraged by the realities of competition and patterns of study section behavior.

#### The Awards Process Revisited

While it is not possible for NIH to reverse the trends of fiscal constraints that have been responsible for many of the difficulties I have been discussing, we are examining carefully the question of whether certain attributes of the current extramural award system may be making the grants application process more burdensome than necessary for the investigator, the university, and the NIH peer review system. We are also looking into the question whether our current mechanisms or systems contribute to uncertainty and instability in the careers of scientists and create impediments to their productivity. It has been suggested, for example, that one of the factors that may be contributing needlessly to the workload of both the grant applicant and the NIH peer review system is the excessive complexity and sheer bulk of the research grant application. Inasmuch as the NIH peer review system is itself made possible only by generous contributions of the time of non-Federal scientists, we must be sensitive to any unnecessary compounding of their task as well as the task of the applicant.

It was also observed in a recent study that only about 40 percent of the principal investigators who received their first NIH project support were able to compete successfully for continued NIH research grant support. In part to remedy this problem we are encouraging first-time applicants to

ask for support for an adequate length of time, as much as five years when needed, to conduct the research being proposed. Our study sections and advisory councils have been asked to cooperate in this initiative to make it possible for meritorious, newly-independent biomedical investigators to have sufficient time to develop their research capabilities and demonstrate the merit of their research ideas. We see this step as a means for diminishing the inefficiency and waste of intellectual resources created by the need for investigators to expend relatively large amounts of time and effort in applying at too frequent intervals for support. This action helps to correct the possible inequity created by requiring a new investigator to justify continued research support when that individual has only a limited time in which to produce evidence of research accomplishments.

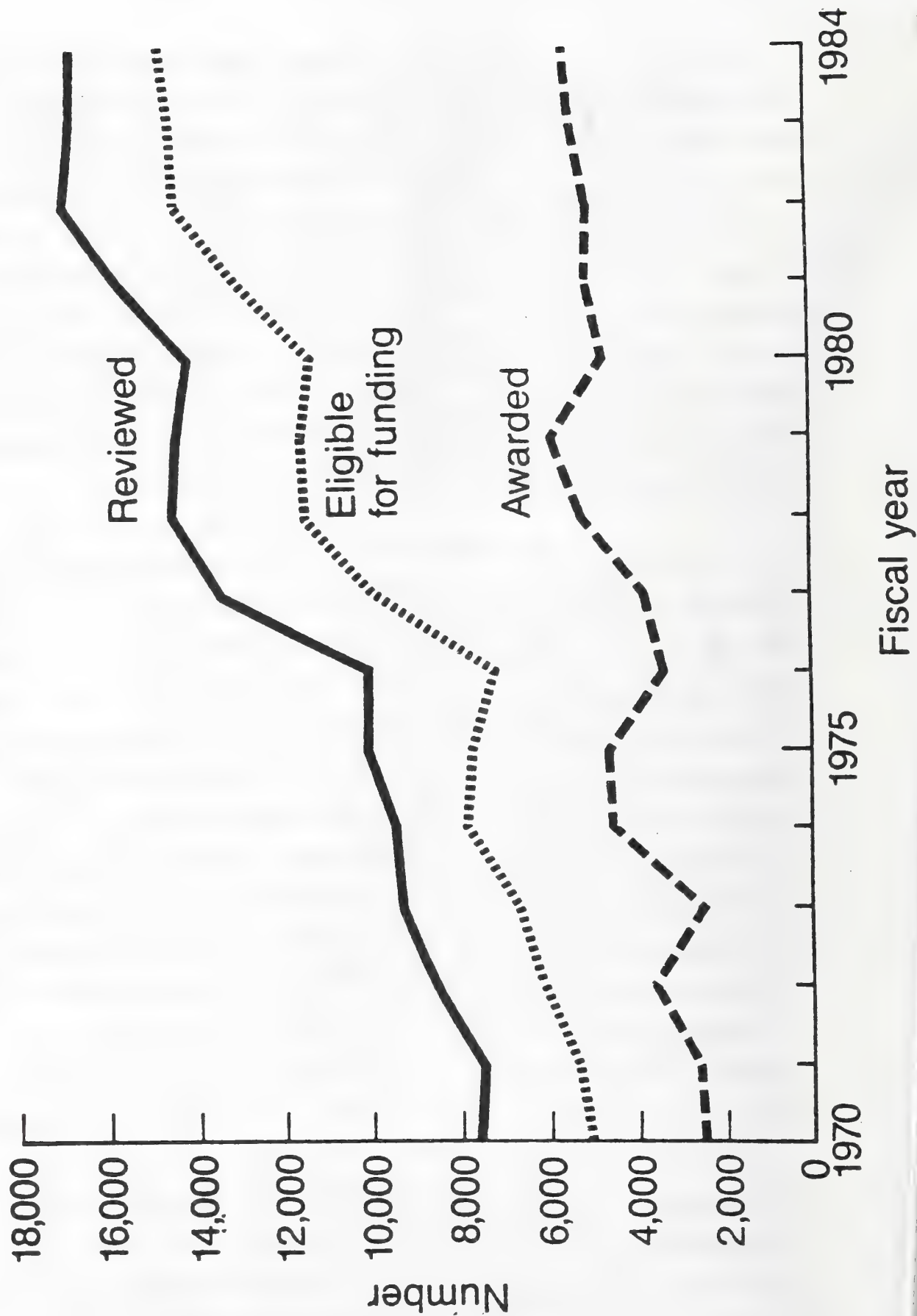
In recognizing the unique strengths of established investigators, ways are being considered to provide longer, more stable research grant support for highly meritorious scientists, and to modify the criteria and methods by which they are selected for continued support. A pattern for this approach has been established by the Javits awards being made by the National Institute of Neurological and Communicative Disorders and Stroke. These awards are made for periods of seven years to outstanding mid-career scientists on the basis of merit. We wish to establish this type of award NIH-wide during 1986. We believe that longer mid-career grants to such established investigators would represent an efficient and prudent investment of Federal funds. But the suggested reforms entail more than administrative adjustments. Their budgetary consequences can be substantial and in the absence of major funding increases could reduce the number of new and competing renewal grants we would be able to make in future years.

#### Research Training

I would like to turn briefly to another subject--an essential component of NIH activities: research training. There are two general categories of NIH training programs--namely, those funded through the National Research Service Awards (NRSA) and those encompassed in the more advanced career development series. NRSA institutional awards permit institutional selection of trainees at both the predoctoral and

# NIH RESEARCH PROJECT APPLICATIONS, 1970-84

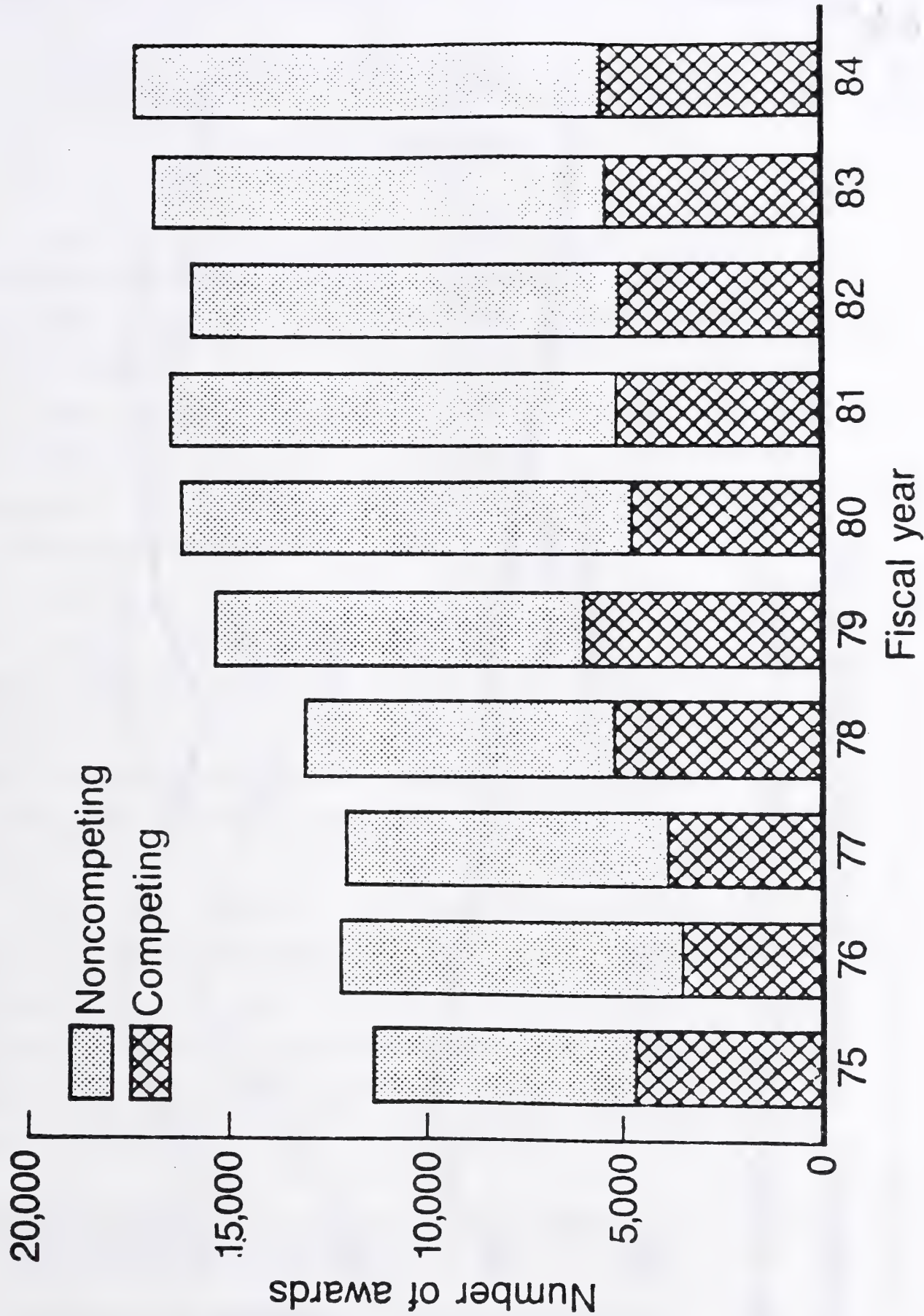
SLIDE 3





# NIH RESEARCH PROJECT GRANTS, 1975-84

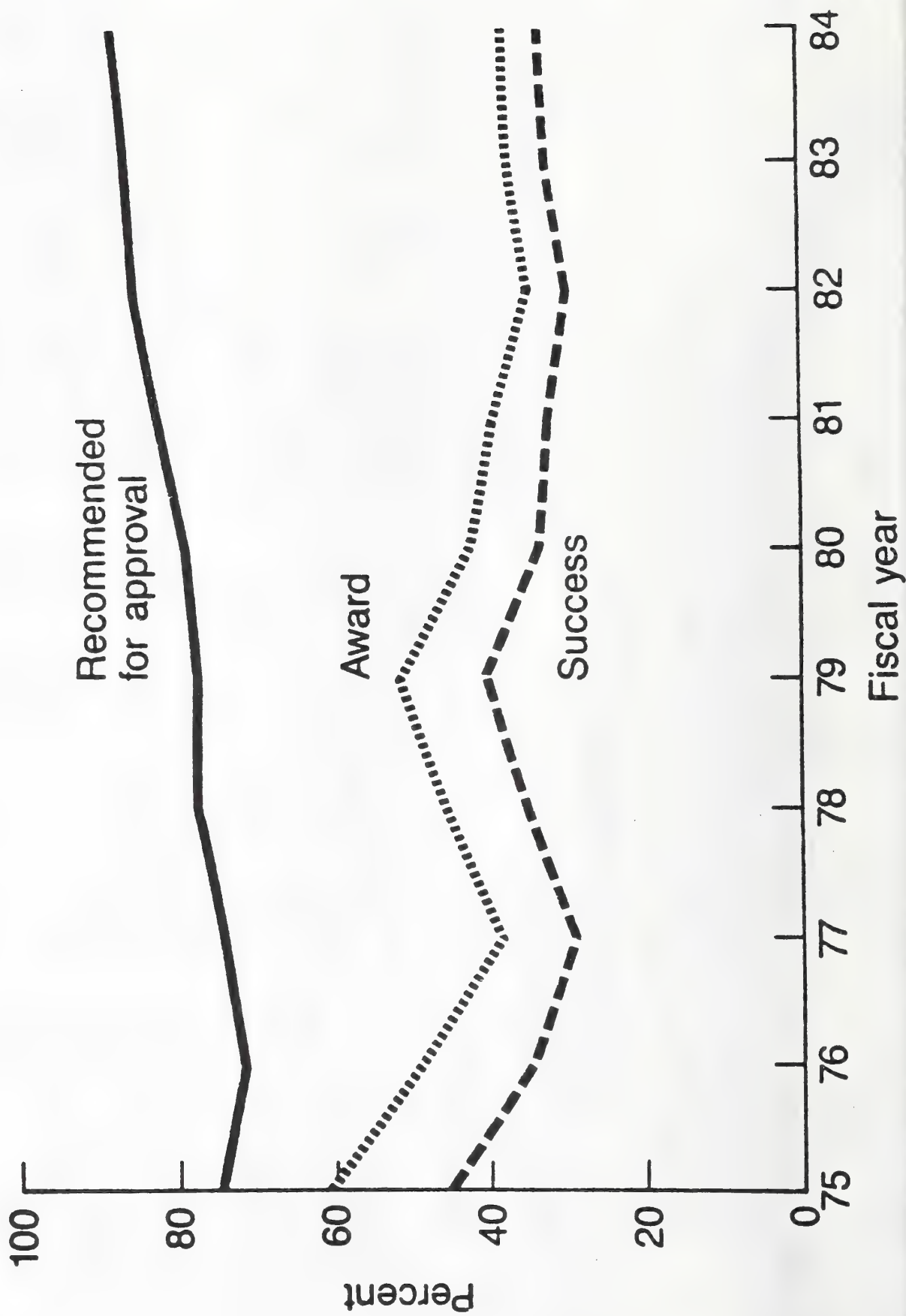
SLIDE 4





# APPROVAL, AWARD, SUCCESS RATES OF NIH RESEARCH PROJECT APPLICATIONS, 1975-84

SLIDE 5



NIH SUPPORT OF RESEARCH AND RESEARCH TRAINING IN NEUROBIOLOGY\*

by

James B. Wyngaarden, M.D.\*\*

There seems to be no better way to characterize current advances in the neurosciences than to refer to them collectively as an explosion of knowledge. And the force of this explosion grows stronger. We are well on our way to learning how the brain and nervous system function in health as well as in specific illness. The pace of basic and applied research on a full range of questions in the neurosciences is unprecedented. This level of activity is gratifying not only from a scientific but also and especially from a humanitarian perspective. Such work is critically important because disorders of the nervous system are not only life threatening but also can seriously compromise the quality of life.

Further, this area of medicine is unusually challenging inasmuch as few neurological disorders are yet preventable or curable. With drugs or medical devices we can control the symptoms of some diseases, such as epilepsy or hearing loss. But for the great majority of patients with neurological and communicative disorders, current medical knowledge can only ease symptoms. As members of the medical and research communities, we share a common commitment to change this state of affairs. The pathway to such change and to the advances in the neurology of tomorrow is research.

I will report to you on the NIH support of research and research training in neurobiology, and particularly on the activities of the National Institute of Neurological and Communicative Disorders and Stroke. In keeping with the future-oriented theme of this symposium, it is appropriate to mention a list of topics considered as "Research Areas of Excitement." The NINCDS director, Dr. Murray Goldstein, used the list during our most recent budget hearings in discussing with the Congressional Appropriations Committees the institute's plans for the coming year.

---

\*Address given at the American Neurological Association meeting, Chicago, Illinois, October 5, 1985.

\*\*Director, National Institutes of Health, Bethesda, Maryland

The eight areas of special research interest are:

- o The biology of the neuron.
- o The biology and pathology of the receptor.
- o Metabolic imaging of the brain.
- o Selective vulnerability, that is, a study of the disease processes that attack specific portions of the brain or central nervous system, initially harming only that portion but eventually reverberating throughout the body--for example, parkinsonism, ALS, Huntington's disease, Alzheimers, and presbycusis.
- o The fifth topic of special interest is neural repair--axon regeneration.
- o Infectious particles.
- o Immunological factors--autoimmune dysfunction.
- o And finally, replacement therapy, CNS implantation, and neural prostheses.

It is more than likely that some of these topics will continue to be challenging tomorrow and possibly the day after tomorrow, but who could have predicted that we could watch the living brain at work with such non-invasive tools as positron emission tomography or magnetic resonance imaging. Or who could have predicted the speed with which we could locate the genetic marker for Huntington's disease. For perspective on the rate of progress, it is well to remember that ten years ago we knew of a half dozen neurotransmitters; that now we know of 50, and in the future we may know of hundreds.

To correlate particular advances in new knowledge with specific levels of investment in research is unrealistic. On the other hand, it seems clear that the broad advances being made in the neurosciences are attributable in the main to the emphasis that in recent years has been placed on the conduct and support of research in this area.

While the secrets of nature are not revealed upon demand--no matter how much is invested to discover them--we are all aware of the great rewards that research time, effort and funds can yield when applied to a

field that is ripe for such study. That seems to be the situation that has pertained in the neurosciences for the past decade, and the opportunities for further advance seem brighter than ever.

In 1975 the appropriation for the National Institute of Neurological and Communicative Disorders and Stroke was \$142 million, and by 1985 it had increased to almost \$397 million, a change of more than 178 percent. During that same time span, the total NIH budget had increased at a somewhat slower rate--that is, 146 percent.

The budgets of the various components of the NIH reflect judgments made by the program scientists, the administrators of the institute, the NIH, the Department of Health and Human Services, the Office of Management and Budget, the President, and the Congress. When an institute receives above average increases for a decade, as was the case with NINCDS, it is an indication that there is a widely shared sense of scientific opportunity.

The level of activity of the scientific community in the neurosciences is also a reflection of such heightened interest. In 1975, a total of 984 applications was received by NINCDS for support of investigator-initiated research projects. In 1984, the total of applications came to 1,798, an increase of 72 percent. The overall increase of grant applications received by NIH as a whole was 66 percent during this same period. As measured by the number of research proposals submitted, as well as by increase in budget, the level of activity in the neurological sciences has exceeded the average of all biomedical disciplines during the past decade--a time of general ferment in all of the biosciences.

This increased level of activity in all components of the biosciences--an effect of the progress of science--has brought with it new pressures on the NIH. The number of excellent applications for grants increased at a much more rapid rate than our ability to fund them. The number of competing applications for project grants reviewed in 1984 was 16,900, essentially double the number reviewed in 1971. In 1985, just completed, the total was about 19,500.



In the past decade, we have become increasingly concerned about maintaining a relatively stable and predictable level of new and competing renewal project grants. The number of competing awards has fluctuated greatly since 1970, ranging from a total of 2,580 in 1970 to a projected high of almost 6,250 in 1985. Such fluctuations not only create financial problems for grantee institutions but adversely influence the career decisions of graduate students as well as young scientists.

We have recognized that to assure future health gains, the current national research capability must be sustained and enhanced. As applied to research project grants, a major goal was to minimize the year-to-year fluctuations in the number of competing grants. The goal of funding at least 5,000 new and competing renewal grants atop a base of moral commitments of 11,000 continuation grants was considered a major feature of the "stabilization" policy. While we have indeed supported at least 5,000 competing research project grants each year since 1980, budgetary limitations have precluded a comparable degree of stability for other research and training programs of the NIH.

In the period from 1972 to 1984, the budget for research project grants increased from 44 to 66 percent of the extramural budget and that for all research grants from 66 to 85 percent. There was a concomitant reduction in budget for research contracts and research training--compressed to about 15 percent of the extramural budget.

One of the highest priorities of the NIH and of the NINCDS in particular, is the promotion and sponsorship of research training. The programs designed for that purpose in the NINCDS are aimed at developing a cadre of skilled investigators capable of applying the modern research tools of neurobiology to the investigation of neuronal mechanisms. Emphasis has been given to training in: the basic neurosciences, including molecular biology, developmental neurology, neurobiology, neurochemistry, neuroimmunology, neuropharmacology, neurovirology, and the basic communicative sciences.

The NINCDS gives special emphasis to the recruitment and research training of clinical investigators in the neurological and communicative disorders. The program supports training for research careers aimed at the development and evaluation of improved methods of diagnosis, prevention, therapy, and the application of experimental animal research to clinical problems of the human nervous system.

Career development in a broad spectrum of research in the neurosciences has been supported in the Research Career Program that includes Research Career Development Awards, Teacher-Investigator Development Awards, and Clinical Investigator Development Awards. Former awardees of these programs are at the forefront of research in the neurosciences. The majority of former awardees have competed successfully as principal investigators on NIH project grants. In particular, the older Teacher-Investigator Development Awards and the newer Clinical Investigator Awards have proven highly effective methods for the recruitment of future clinical investigators in the neurological and communicative disorders.

The importance of the contribution from the latter programs is apparent when the recent history of NINCDS training programs is examined. In 1975 well over 400 physicians were being supported in the traditional NINCDS training programs. In fact, more than half of all the institute's trainees were then physicians. With the discontinuation of support of neurology residency training programs, and the advent of National Research Service Awards as the major training instrument, the total number of NINCDS trainees dropped sharply from about 800 to about 500 in 1977 and since that time has remained fairly stable in the range of from five to six hundred.

In 1977 the number of physicians in NINCDS research training under NRSA had dwindled to around 50 as those in previous clinical programs completed their programs and were not replaced. Only recently has the number begun to climb and by 1985 had reached 93, or roughly 18 percent of the total trainees.

The percentage of NIH research grants held by M.D.s has also fallen progressively over the years. In the 1960s, M.D.s held about 45 percent of all NIH grants. Currently M.D.s hold only about 22 percent.

The decline in absolute number of M.D. investigators working under project grants reflects in part the submission of relatively fewer grant applications by M.D.s. Another important factor is the intense competition. During the past 15 years new M.D. applicants have competed much less well than new Ph.D. applicants, with both groups competing less successfully than the M.D./Ph.D. applicant.

The simplistic explanation that greater difficulty is inherent in working with human subjects is probably not the answer to the lower approval rates for clinical research proposed by physician investigators. For as we know, science has become complex and the methods intricate. The standard two or three-year fellowship, often consisting of a mix of research and subspecialty training, is no longer adequate preparation. Such an M.D. trainee remains less well trained than the Ph.D. scientist who has been training for a research career since the baccalaureate degree. In my view, the trends of the past two decades reflect the progressive professionalization of biomedical research, in particular of clinical research. I hope that there will always be room for the creative amateur in clinical investigation, but history indicates that such a person is less likely to secure external support for his or her work. Success for an M.D. investigator is increasingly dependent upon substantial training--three to five years--in the information, concepts, and methodologies of complex modern science. To be a first-rate scientist and a well-qualified physician is a demanding calling.

Programs have been launched by the Federal Government, by industry, by voluntary health organizations, and by philanthropic foundations for the purpose of increasing the number of well-trained clinical investigators. Several of these initiatives are based on the observation that the curricula of most medical schools provide little or no laboratory experience that is representative of modern day medical science. The rise of specialty fields and the lengthening of postdoctoral training programs have extended the



clinical training necessary for board certification. The requirements of many certification boards are to a considerable degree inflexible and do not encourage the potentially creative physician to enter research training.

The NIH has special interest in training programs that provide medical students, who are interested in research, early exposure during the course of their professional training.

An innovative addition to NIH program resources is the joint NIH-Howard Hughes Medical Institute Scholars Program. In this activity, whose purpose is to attract medical students into research, the Howard Hughes Medical Institute will support the research training of 25 to 30 medical students at NIH for from nine months to a year following their second year in medical school. The joint agreement provides for funding by the Hughes Institute for stipends and travel expenses for the trainees who will participate in research activities in our intramural laboratories, side by side with some of NIH's leading scientists. The Hughes funding will also make possible a structure on the NIH campus for living quarters, classrooms, and teaching laboratories. The first class of 23 students, selected in nationwide competition, has just entered training at NIH.

We believe that through the portfolio of NIH research training programs, including the successful older programs as well as our newer approaches, we will be effective in increasing physician participation in biomedical research--a matter that we consider to be essential to future progress. Such participation benefits more than science for biomedical research, teaching and patient care are mutually reinforcing activities.

In a moment I will discuss briefly the NIH budgetary situation as we enter fiscal 1986. Before doing so, however, I must mention an issue of special importance in the context of the neurosciences--that is, the use of animals as subjects in research. In the field of neurosciences, and particularly in studies involving the brain, productive research requires animals and especially those of the higher orders. Consequently, questions about animal research are of special concern to investigators in the neurosciences.



In spite of the fact that virtually every major development across the spectrum of biomedical research has depended in part upon the use of animals, many institutions are coming under pressure from a small but determined segment of society opposed to this aspect of research. There have been break-ins at about a dozen sites, a sit-in at NIH, and at other localities there have been bomb threats and vandalism against the property of investigators and others associated with studies requiring animals.

Legislative activities on the subject at national, state and local levels are on the increase. There is a critical need to develop better understanding among the general public, the mass media, and elected officials on the scientific imperatives of using animals in research. It is a time when investigators and administrators must give the most careful attention to their own performance with respect to guidelines and standards on the care and use of laboratory animals.

We remain convinced that the vast majority of biomedical scientists and their institutional officials are committed to maintaining the proper standards. However, material failure by our awardees to meet animal welfare requirements can undermine the credibility of our current assurance system and possibly lead to substantially more restrictive and extravagantly costly methods for the protection of animal subjects. We will continue to foster animal experimentation whenever such research gives promise of improving human health and is conducted in accordance with our animal welfare requirements.

In conclusion, I will report briefly on the status of the NIH budget. For all Federal agencies, Tuesday, October 1, was Fiscal New Years Day. We enter fiscal 1986 without a regular appropriation but on the basis of a continuing resolution set to expire in mid-November. Under the continuing resolution, NIH will continue to operate at the funding level established by the 1985 appropriation until Congress and the President take further action on our budget.

The 1985 budget permitted the NIH to award more than 6,200 new and competing renewal research grants and provide funds for 533 research centers.

Under instructions from the Office of Management and Budget, an additional 200 of the 1985 competing awards are to be made for one year only so that extension of these grants into the second year would count against 1986 allocations for competing grants. Under normal circumstances we fund about 250 one-year grants annually. The OMB instructions would require us to increase that number to 450.

The regular 1986 appropriation for NIH has not reached the floor in either the House or the Senate. However, the full House Appropriations Committee markup was made public September 26. For technical reasons certain programs are not included in the House total of \$5.247 billion, but if they are added at current levels the House Committee total would come to \$5.483 billion, or about 6.5 percent above the 1985 level of \$5.14 billion.

The Senate Appropriations Subcommittee markup of \$5.406 billion was slightly lower than the House.

The House Committee markup included an increase of a bit over 9 percent, or \$36.6 million for currently authorized NINCDS programs. The Senate Subcommittee markup was based on the assumption that certain expiring authorizations would be reinstated. The Senate increase was slightly lower than the House--\$32.8 million, or about 8 percent.

As you know, the final story on the 1986 budget is yet to be written. It will be some time before we know the outcome.

That's about all that can be said about appropriations just now, but I would be happy to respond to other questions you may wish to ask.

# # #



REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

On behalf of the National Institutes of Health, I am pleased to welcome you to this first conference on ethics consultation. It is appropriate that it be held near NIH, where scientists and others have given so much attention to ethical concerns in biomedical research. Group consideration of proposed research has been the practice since the opening of what is today called the Warren G. Magnuson Clinical Center.<sup>1</sup> That procedure exists in a more refined form today, but even then--in 1953, when the Clinical Center opened--weighing the risks and informing the research subject were emphasized.

Group consideration here and elsewhere existed some years in advance of the National Research Act's requirement that Institutional Review Boards be set up wherever Public Health Service funds were used for research involving humans. Today, the NIH Office for Protection from Research Risks oversees 660 IRBs at major institutions and another 2,000 at smaller ones. NIH has also contributed to the work of national commissions, whose members have enunciated a philosophy that has added to the protection of research subjects.

---

\*Opening address, given at the NIH-UCSF Conference on Ethics Consultation in Health Care, Bethesda, Maryland, October 7, 1985.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



As for bioethics in clinical practice, its importance has become apparent only in comparatively recent times. Medicine is The Youngest Science, as Dr. Lewis Thomas has called it.<sup>2</sup> Paradoxically, effective medicine leads to ethical dilemmas. Resuscitation is an example. The technique of controlling ventricular fibrillation by electric shock is less than forty years old; the technique of massaging the chest to make a reluctant heart pump is less than thirty years old.<sup>3</sup> Only a few decades ago, physicians had no reason to discuss whether to respect the patient's and family's autonomy by talking to them about "do-not-resuscitate" orders; resuscitation as we know it today didn't exist.

Other influences leading to an increased emphasis on bioethics are external to medicine, as Dr. Daniel Callahan, of the Hastings Center, has pointed out.<sup>4</sup> Those influences include a rise in concern about the behavior of all professionals, an unease about technology, pressures on the health care delivery system to deal with a whole range of human problems, and an increase in the size and scope of medical research and clinical care. That size and scope in turn attracts much attention, particularly from the media.

I'm gratified to be able to say that health care providers have been leaders in recognizing ethical dilemmas. They have regularized procedures for dealing with many of these dilemmas and have established bioethics committees. Last year a survey by the American Hospital Association revealed that twenty-five percent of all hospitals had such committees,<sup>5</sup> and undoubtedly the percentage is higher today. At least ten percent of

hospices have them, and there is a strong interest in these committees in nursing homes. At their best, the committees may bring the community's conscience to bear on bioethical problems.

And a specialty has sprung up--that of the ethics consultant. What you consultants do, however, isn't completely new. As long as medicine has existed, physicians have discussed with trusted advisors the question, "What is the right thing to do for this patient?" But now ethics consultants have helped develop principles, rules, and guidelines and are applying them. You are introducing consistency into the resolution of some difficult problems.

The NIH Clinical Center, too, has found the need for ethical consultation. A few years ago, that institution's director made a wise decision: he appointed an Episcopal priest who had a strong education in ethics as the Clinical Center's assistant for bioethics. That person--the first to serve in the post--is Dr. John C. Fletcher. Health care providers have found his contribution to be invaluable. He has earned the respect of clinicians, nurses, and others and incidentally has helped reduce the stress that they experience in making hard choices. He and Dr. Maxwell Boverman, as a consultant, form an able team.

You who attend this conference have varied backgrounds. Some of you are philosophers, some are members of the clergy or of religious orders, some are nurses, some are physicians, some are lawyers--and all are bioethicists. That people of many disciplines come to your specialty

makes you the more influential. Your diversity is needed. A sign in one hospital expressed that well. It read, "None of us is as smart as all of us."

You have earned your present status. Patients, families, and health care providers may well be affected by what you accomplish at this conference. The wide interest in the further contribution that you can make is reflected in the fact that the NIH Clinical Center and the Division of Medical Ethics, University of California, San Francisco, are joint sponsors of this conference and that additional funds were provided by the Eberhard Foundation and Blue Cross-Blue Shield. It is clearly appropriate for you to chart how you can serve even more effectively in the future.

I wish you the greatest success in your proceedings. Thank you.

#### REFERENCES

<sup>1</sup>National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, Report and Recommendations: Institutional Review Boards (DHEW Publication No. (OS) 78-0008), pp. 40-41, citing Mark Frankel, The Public Health Service Guidelines Governing Research Involving Human Subjects: An Analysis of the Policy-Making Process (Washington, D.C.: George Washington University Program of Policy Studies in Science and Technology, 1972), p. 9.

<sup>2</sup>Lewis Thomas, The Youngest Science: Notes of a Medicine Watcher (New York: Viking Press, 1983).

- <sup>3</sup>C. S. Beck, W. H. Prichard, and H. S. Feil, "Ventricular Fibrillation of Long Duration Abolished by Electrical Shock," JAMA 135 (1947):985-986. W. B. Kouwenhoven, James R. Jude, and G. Guy Knickerbocker, "Closed-chest Cardiac Massage," JAMA 173 (1968):1064-1067.
- <sup>4</sup>Daniel Callahan, "Shattuck Lecture--Contemporary Biomedical Ethics," N Engl J Med 302 (1980):1228-33.
- <sup>5</sup>"Hospital Ethics Committees Surveyed," Hospitals 58 (1984):52.





180

ADDRESS\*

by

James B. Wyngaarden, M.D.\*\*

I am very happy to be here today to speak at the Industrial Biotechnology Association (IBA) annual meeting. In past years, it has been quite common for NIH directors to address primarily university or medical school audiences or professional societies of various scientific disciplines. But in the past two years, it seems, I have spent equal time either speaking before industry-related groups or to academic audiences about issues and science relating to commercial concerns.

This, of course, is due to increased interest in what we have come to call the "new biotechnology"--the tremendous enthusiasm surrounding the expected payoff from this field, coupled with a deep commitment to safe applications. The fact that industry, academia, and government are cooperating so closely on the diverse and complicated issues surrounding the launch of this new era is gratifying. This level of cooperation--which is particularly high on the part of the IBA and its member companies--is certainly healthy and will help in maintaining dominance in this field for the U.S.

---

\*Presented at the Industrial Biotechnology Association annual meeting, J. W. Marriott Hotel, Washington, DC, October 10, 1985.

\*\*Director, National Institutes of Health, Bethesda, MD

For its part, the NIH would be enthusiastic about the concepts and methodologies of the science undergirding biotechnology even absent the commercial promise. For this new science has advanced our understanding of biological mechanisms and processes in health and disease in ways that are unprecedented. Now, thanks to laboratory techniques such as recombinant DNA technology, we are beginning to make headway toward effective vaccine development in several recalcitrant fields. This is but one example. Biotechnology has had an impact on the conduct of basic biomedical research comparable, perhaps, to that of the computer on information processing. Biotechnology has moved us ahead by leaps and bounds in understanding cancer genetic defects, organ transplantation biology, clinical immunology and the allergic response, and bone development and repair, just to name a few areas.

The competitive advantage this country currently holds in biotechnology is in part due to the investment of NIH over the years. In its recent report on commercial biotechnology, the Office of Technology Assessment (OTA) concluded that three factors are of overriding importance in determining a country's competitive position in world markets.<sup>1</sup> Two of those three factors--funding of basic and applied science and the supply of adequate numbers of trained personnel--have been and remain a major commitment of the NIH. The third factor, availability of funds for industrial development, of course, is the responsibility of others. In its comparison of competitor countries in

biotechnology, the OTA report determined that the U.S., both in absolute dollar amounts and in relative terms, has the largest commitment to basic research in the biological sciences. The OTA report also concluded that the U.S. currently has a competitive edge in the supply of molecular biologists and immunologists able to meet corporate needs, in part because the U.S. Government has provided substantial funding since World War II for basic life sciences research and research training in U.S. universities.

NIH continues to make a major commitment to the future of biotechnology--in Fiscal Year 1985, it is estimated that the NIH will have provided approximately \$600 million for basic research and research training directly related to biotechnology and almost \$1.3 billion for support of the broader science base underlying this field. By basic research directly related to or utilizing the new biotechnology, we mean genetic manipulation, cloning of DNA, use of special techniques to isolate and detect DNA, creation of hybridomas and production of monoclonal antibodies, and computer methods used to analyze DNA and protein sequences. Basic research underlying the new biotechnology includes undifferentiated free-ranging investigations in genetics and molecular biology, cell biology, and immunology.

Of the figures I mentioned, \$31 million in Fiscal Year 1985 is for training directly related to biotechnology and about \$54 million for training in the broader science base. In 1983, it is estimated that NIH supported 1,500 predoctoral trainees,



approximately 350 postdoctoral trainees, and more than 600 individual postdoctoral fellows in biotechnology and related areas. From 1979 to 1983, there has been an upward trend in both expenditures and the total number of individuals receiving training.

The proportion of the total NIH budget devoted to biotechnology has remained constant since 1983--with about 11 percent devoted to directly related research and about 25 percent devoted to underlying basic research and research training.

One especially interesting indicator of the U.S. preeminence in this field, built on government support of basic genetic research, is the distribution of Nobel Prizes--30 of the 46 Nobel Prizes awarded between 1958 and 1984 for work in the basic science underlying biotechnology were won by American scientists. All but one of the American scientists received either research training or research support from NIH at some time during their careers. Of the 17 foreign Nobelists, 8 were supported for a period by the NIH.

In assessing what we would term our success in the past 10-20 years in advancing basic knowledge in the many disciplines related to biomedicine, however, it is necessary to look beyond mere dollars invested in research and training. Since the time NIH began to develop its extramural programs--after World War II--we

have adhered to several principles that have served us well over the years.

Foremost is the conviction that basic knowledge should be pursued largely through the support of biomedical research conducted by scientists at universities, and that the capacity of those university departments (primarily medical schools) should be strengthened wherever possible. Another guiding principle has been that the primary source of research support should be the investigator-initiated research project grant, by which mechanism we believe we can tap the most creative minds attacking the most critical problems in science.

A third important factor has been our reliance upon a peer review system of outside advisors for selection of the most meritorious proposals presented to us. This so-called dual review of grant applications consists of two sequential levels of review--first by panels of experts established according to scientific disciplines, which have as their primary function the review and evaluation for scientific and technical merit, and second by the statutorily mandated National Advisory Councils or Boards attached to the NIH bureaus, institutes and divisions that actually make awards. The council recommendations are based not only on considerations of scientific merit, but also on the relevance of the proposed study to the NIH programs and priorities.

Over the years, this system has worked amazingly well. This review process has selected research for support that has led to important discoveries: the identification of restriction enzymes to cleave DNA selectively; procedures for introducing specific pieces of DNA into bacterial cells; the use of enzymes to join pieces of DNA; methods for isolating and visualizing pieces of DNA and calculating their size; and procedures for determining nucleotide sequences, for producing synthetic nucleotide sequences, and for selectively modifying DNA. All of these discoveries have already contributed to the advancement of the field of biotechnology.

Another major NIH contribution to the advancement of biotechnology has been our early involvement in guiding the new technology toward public acceptance. As some of you will remember, the NIH became involved in policy formulation for the conduct of this new science long before the term "biotechnology" was a part of our everyday language. This was in 1974 when few--certainly not the general public--knew very much about the promises and potential perils of recombinant DNA research. Impelled by public, scientific, and congressional pressure attending the matter, the NIH--which traditionally has shunned a regulatory role--rather reluctantly took on responsibility for organizing a mechanism for setting safety guidelines. This was the Recombinant DNA Advisory Committee (the "RAC"), which began to develop proposed guidelines for recombinant DNA research carried out with NIH funding. These were designed to permit research to

continue with minimal constraints, yet protect the public interest, with a good measure of responsibility at the institutional level. The RAC was the mechanism that served to relieve public pressure on the issue of genetic engineering and to permit early experiments to proceed. Moreover, the RAC, as it has evolved today, is serving as a model for the development of similar bodies in areas of biotechnology specific to the interests of other government agencies. Some of the key characteristics of the RAC that have made it so successful include its reliance on participation from academia, other relevant government agencies, and recently from industry; its practice of case-by-case risk assessment of proposals; and its insistence, in almost all cases, open meetings.

Although the NIH has contributed greatly to the solid foundation of the fledgling biotechnology, we do not intend to become complacent. As far as NIH is concerned, the budget has continued to grow every year since 1968, with purchasing power up 2 percent after adjusting for inflation. Our commitment to basic research remains high. In FY 1985, 62 percent of NIH's budget was devoted to basic studies, an increase of 10 percent over that allocated to basic research in 1980.

With regard to training, there is some indication that although the U.S. now has a competitive edge in trained researchers in disciplines applicable to biotechnology, we may face a shortfall in the future as biotechnology firms begin to



hire more well-trained specialists than are being produced by our universities. This shortfall could harm the academic biomedical research enterprise and education in the biomedical sciences, since we would lack adequate faculty to teach and train the technologically competent work force needed to maintain and further develop the competitive position of the U.S. in biotechnology.<sup>2</sup> The fact is, no really reliable data exist on industrial personnel needs for the future, and any information that might be gathered by the IBA would be very useful to all concerned.

It is clear that if we expect to hold our competitive position in biotechnology, we need examine our current efforts with an eye toward the future. For this reason, in June of this year, I asked the NIH Director's Advisory Committee to set aside two days to discuss in a public forum the proper role for the NIH in the arena of biotechnology policy. I asked the members and invited speakers--one of whom was Dr. Price--to address the following questions: What should be the role of NIH in the support of generic research of direct relevance to biotechnology? Are there special training needs that can be addressed by the NIH? And what other activities might appropriately be undertaken by the NIH to further the goal of promoting biotechnology?

It was my expectation that the group would help to sort through and identify a set of activities representing a logical and natural extension of the current NIH capabilities, in an effort to enhance the NIH contribution to the development of a

strong U.S. biotechnology industry. In my opening remarks I pointed out to the advisory group that in the past, NIH has demonstrated flexibility in extending its mission boundaries in selected areas to meet special needs, while guarding against serious distortions of its basic mission or jeopardizing the integrity of its traditional programs. This sort of mission expansion, however, particularly in the face of a steady state budget, is something that would be undertaken only with great care and deliberation.

The invited guests from academia, industry and government gave thought-provoking talks, rich with a myriad of suggestions for NIH. Some of the suggestions included the following:

- That NIH give additional emphasis to areas outside the biomedical realm, for example, to the sciences relevant to plant and agricultural biotechnology.
  
- That NIH support generic applied or "bridge research"--that is, the science bridging the gap between basic and product development research, including bioprocessing technologies. In its study, the OTA concluded that if the U.S. scaled up its efforts in bioprocessing, this would greatly help the U.S. compete with Japan. It has been estimated that the U.S. spends about 1 percent of its research budget on generic applied research, while Japan spends 50 percent.

Other suggestions were:

- That NIH increase the manpower pool in molecular biology, molecular genetics, immunology, and virology, and that NIH encourage U.S. postdoctoral training abroad.
- That NIH find ways to enhance the movement of scientists between industry and government.
- That NIH increase support for the Nation's research infrastructure--that is, for buildings and facilities.
- And that NIH establish a subdivision within each of its research components to promote biotechnology.

A recurring theme heard throughout the two-day meeting might serve as my summary of the group's consensus: that NIH ought to continue to do what it does best--that is, support research and research training in biomedicine--but also be open-minded and flexible as to how we might further contribute to the future of biotechnology. In addition, they concluded, it would be well to examine the areas where NIH's boundaries might be made more elastic in responding to concerns that surround the issue of industrial competitiveness.

All the recommendations from the meeting have been turned over to a special internal NIH committee headed by Dr. Ruth Kirschstein, Director of the National Institute of General Medical

Sciences (NIGMS), that component of NIH responsible for support of basic genetic research. She and her committee will be working with the material from the meeting and returning to me with concrete policy recommendations.

In the meantime, we have already taken a number of actions that relate to the suggestions made: We are participating with the National Science Foundation in support of a biotechnology program at MIT whereby engineers are being trained in areas relevant to bioprocessing. Our role in that program is small at the present time.

The NIH is particularly interested in encouraging industry-government collaborations. We will be holding major briefing sessions for chief executive officers of biotechnology firms so that they can become more familiar with our programs as we learn more about how we might increase cooperation. We are also planning a two-day seminar at the NIH so that industry scientists might visit NIH labs and meet our leading intramural scientists.

The NIH has developed a new consultancy policy to permit our intramural scientists to consult with industry--under certain guidelines regarding conflicts of interest--and receive honoraria. This is not seen as an opportunity for an intramural scientist to share his or her most recent experiments with industry on a selective basis, but rather an opportunity for industry to tap that scientist's general knowledge and expertise in a field of



interest to the industry. Heretofore, it was not possible for an NIH intramural scientist to have any kind of continuing contact with industry in this way. In addition, we are open to the possibility of more scientists from industry working in our intramural laboratories for periods of time.

The NIH intramural program in many ways constitutes a rich resource for research and research training in biotechnology. Just recently we developed a proposal for a Research Associateship Program in Biotechnology to increase opportunities for cooperative research, to provide postdoctoral scientists with additional research training in biotechnology, and to expand access to government laboratory facilities and resources.

For individual working scientists in the field of biotechnology, NIH supports several major projects: Bionet--a national computer resource for molecular biology which gives researchers ready access to national databases on DNA and protein sequences and provides a library of sophisticated software for sequence searching, matching and manipulation. This resource will be instrumental in fostering interaction among a community of molecular biologists who can communicate rapidly, effectively, and frequently over a computer network.

The NIH also supports the Human Genetic Mutant Cell Repository, which provides investigators with well-characterized

cell lines from patients with genetic diseases, and GenBank, which is a computerized data bank of all published nucleotide sequences.

I mentioned earlier in my talk the role that the Recombinant DNA Advisory Committee--the RAC-- played in defusing early public concern about laboratory containment of recombinant DNA molecules being utilized in research. Now, as the first products of this new industry are beginning to move from the laboratory to the marketplace, biotechnology is again the subject of heightened public interest and concern. I would like to bring you up to date on a few of those issues as they relate to NIH.

One current issue is that of the deliberate release of organisms containing recombinant DNA in field tests. One proposed project, which had been approved by NIH, is on hold, pending the outcome of a suit filed in 1983 that sought to halt this project involving the field testing of bacteria genetically engineered to increase frost resistance in plants. While this matter remains unsettled and this proposed experiment has not yet been undertaken, the whole issue of review of this type of research has been widened. The EPA has determined that such experiments require EPA approval.

A second current issue is that of human gene therapy using genetic engineering techniques. At a meeting just last month, the RAC unanimously approved a document entitled "Points to Consider in the Design and Submission of Human Somatic Cell Gene Therapy

Protocols," prepared for the purpose of guiding scientists considering gene therapy in human subjects. Public comments on the draft document were sought during its developmental stages, and based on the comments received, changes were made in the final version.

The genetic research covered in the document involves transplanting genes into a patient's body cells to correct an otherwise incurable disease. The therapy in question is limited to somatic cell gene therapy. The document approved by the RAC specifically excludes any experimental treatment that is designed to produce effects in germ cells that would pass from one generation to the next.

In the just approved document, the "points to consider" are largely in the form of questions that investigators will be required to answer in future applications to the RAC and the NIH requesting approval of specific somatic cell gene therapy protocols. According to this guidance, any such human gene therapy experiments would require approval from the investigator's own Institutional Review Board and Institutional Biosafety Committee prior to RAC and NIH consideration.

This action by the RAC is an important step in bringing gene therapy into practical use. Now that the guidance is established, the several scientific teams studying gene therapy can proceed to proposing specific trials with patients.

As many of you know, another policy matter relating to biotechnology remains in a state of flux at present and is indicative of the great and diverse potential of this field. That matter concerns the regulatory posture of a number of Federal agencies such as EPA, FDA, USDA, and others over genetically-engineered materials and products.

The NIH has been concerned about the future role of the RAC, stimulated in part by our understanding of the great potential for biotechnology beyond the usual biomedical interests of NIH.

The RAC itself has discussed the proper boundaries for continued NIH and RAC oversight of recombinant DNA technology: Should the NIH Guidelines be limited strictly to work done in the laboratory? In this case, release into the environment, including field tests, would fall outside the jurisdiction of the Guidelines. Should NIH accept for review only individual proposals funded by NIH or only proposals funded by the Federal government? In this case, review of individual proposals from industry would fall outside of the Guidelines. Should the Guidelines be limited strictly to biomedical research? In this case, agricultural and other studies would fall outside the jurisdiction of the Guidelines.

Recently, as many of you know, these "boundaries" discussions have been elevated to a higher level in the government, in a major



effort to forge a comprehensive and coherent regulatory policy concerning the biotechnology industry. A Cabinet level working group, headed by the White House Office of Science and Technology Policy, on December 31, 1984, published in the Federal Register a "Proposal for a Coordinated Framework for Regulation of Biotechnology." The IBA and individual biotechnology firms have commented on the draft document. In that document it was proposed that the Environmental Protection Agency, Food and Drug Administration, U.S. Department of Agriculture, and National Science Foundation would establish scientific advisory committees, like the NIH RAC, and that over the five committees, there would be created a Biotechnology Science Board--organizationally located in the Office of the Assistant Secretary for Health, Department of Health and Human Services.

At the most recent meeting of the RAC--on September 23--Bernadine Healy, the Deputy Director of OSTP, publicly presented a new configuration for coordination of the five agency-based science advisory committees. Instead of a biotechnology science board there would be a committee composed entirely of government officials established under the Federal Coordinating Council for Science Engineering and Technology (FCCSET). The details of this new FCCSET Committee are still being worked out.

Clearly, the framework for regulating biotechnology remains under discussion, with a great deal of interest and input from private industry. All parties concerned are aware of the need to

maintain a healthy environment for the development of biotechnology in this country so that this country's present international preeminence is not undermined.

In the coming years, I would predict, there will be continued evolution of biotechnology policy and heightened interest in the promises of practical applications in this area of science. Permit me to quote an arresting statement by Nobelist Arthur Kornberg in a speech last year on biology and technology. He said, "I am confident that within five years the most exciting prospects for medicine and industry will be subjects and products that no one now even talks about."

In an era of such great scientific opportunity, there is more than enough room for government, industry, and academia to engage their full resources and energies both in support of the science undergirding biotechnology and in the formulation of policy to guide the future of the industry.

References

<sup>1</sup>Commercial Biotechnology: An International Analysis, Congress of the United States, Office of Technology Assessment, January 1984.

<sup>2</sup>Statement of Gerald D. Shockman, on behalf of the Public and Scientific Affairs Board of the American Society for Microbiology to the Committee on National Needs for Biomedical and Behavioral Research Personnel of the Institute of Medicine, National Academy of Sciences, May 10, 1984, Washington, D.C.

187

COMMENTS\*

by

James B. Wyngaarden, M.D.\*\*

Professor Okamoto, Ladies and Gentlemen,

On behalf of the National Institutes of Health, I wish to express my appreciation to our Japanese colleagues for the gift of this stone lantern in recognition of longstanding cooperation between the United States and Japan in basic research on hypertension.

This stone lantern will serve as a lasting reminder to all of us of the importance of international cooperation in biomedical research. We will select an appropriate site for it so that in the future, Visiting Scientists and others who come to the National Institutes of Health will be able to enjoy the lantern, along with those of us who are at NIH full time.

The U.S.-Japan cooperation in hypertension has contributed significantly to progress in this important field of medicine, not only in basic research but also in developing new information on the prevention and control of this disorder.

I am very pleased that this cooperation has made possible many of the achievements reported on at this international meeting. Professor Okamoto's generosity in sharing these animal models with the National Institutes of Health made possible many of our own contributions to this field of research. By maintaining and, in turn, donating the SHR animal models to hypertension researchers throughout the world, NIH scientists have made progress not only in their own research but also have facilitated the work of their peers in other countries. As a result, we have all profited and science has advanced.

As Director of the National Institutes of Health, I am particularly encouraged to see that the results of these cooperative efforts have led to many outstanding achievements in basic research on hypertension. We are proud to count Professor Okamoto, Professor Folkow, and Professor Snajdar among the scientists whose work has been supported by the NIH. We are pleased that this work has been recognized by their international peers at this meeting. The fact that four different countries--Sweden, the U.S.A., Australia, and Japan--are represented in this award ceremony underscores the importance of international cooperation in the progress of medical science.

Thank you again.

---

\*Acceptance of Stone Lantern presented by Professor Kozo Okamoto to the National Institutes of Health, at the 5th International Symposium on SHR and Related Studies, October 20, 1985, in Kyoto, Japan.

\*\* Director, National Institutes of Health, Bethesda, Maryland.



107

## COMMENTS\*

BY

JAMES B. WYNGAARDEN, M.D.\*\*

PROFESSOR OKAMOTO,

IT IS INDEED A PLEASURE FOR ME TO BE HERE ON THE OCCASION OF YOUR 77TH BIRTHDAY AND TO PARTICIPATE IN THIS INTERNATIONAL SYMPOSIUM HELD IN HONOR OF YOUR CONTRIBUTIONS TO MEDICAL SCIENCE. PRESIDENT REAGAN HAS ASKED ME TO CONVEY HIS PERSONAL CONGRATULATIONS AND TO HAND CARRY THIS LETTER TO YOU IN RECOGNITION OF YOUR ACHIEVEMENTS. LET ME READ THE PRESIDENT'S LETTER TO YOU:

DEAR DR. OKAMOTO,

IT GIVES ME GREAT PLEASURE TO SEND YOU MY CONGRATULATIONS ON THE OCCASION OF THIS INTERNATIONAL SYMPOSIUM CELEBRATING YOUR 77TH BIRTHDAY.

---

\*PRESENTATION OF PRESIDENT REAGAN'S LETTER TO DR. KOZO OKAMOTO ON THE OCCASION OF HIS 77TH BIRTHDAY, 5TH INTERNATIONAL SYMPOSIUM ON SHR AND RELATED STUDIES, OCTOBER 20, 1985, KYOTO, JAPAN.

\*\*DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND, USA.

YOUR TRAILBLAZING CONTRIBUTIONS IN THE  
FIELD OF GENETIC RESEARCH HAVE PAVED THE WAY  
FOR MUCH OF THE TREMENDOUS PROGRESS RECENTLY  
MADE AGAINST STROKES AND HEART DISEASE. YOU  
HAVE THE SATISFACTION OF KNOWING THAT  
THROUGH YOUR EFFORTS THOUSANDS OF PEOPLE THE  
WORLD OVER NOW LIVE LONGER AND HEALTHIER  
LIVES.

ON BEHALF OF THE AMERICAN PEOPLE, I  
JOIN THIS DISTINGUISHED ASSEMBLAGE IN  
SALUTING YOUR FINE ACHIEVEMENTS. GOD BLESS  
YOU!

SINCERELY,

RONALD REAGAN

KOZO OKAMOTO, M.D.  
KYOTO UNIVERSITY



## THE GOVERNMENT'S RESPONSE TO THE AIDS CRISIS\*

by

James B. Wyngaarden, M.D.\*\*

I am very happy to have the opportunity to address this group about the response of the Federal government--especially the National Institutes of Health--to the challenge presented by the acquired immune deficiency syndrome (AIDS). Scientists, many of whom are either employed or supported by the Federal government, have made major contributions in advancing the science surrounding this disease in an amazingly short period of time. But there remains a vast uncharted territory to conquer before we can hope to manage this problem.

Probably you are all aware of the recurring criticism of the government for its response to the AIDS problem. Since the time that AIDS was first described and recognized to be a serious threat, there has been criticism that the government--that is, the Public Health Service and its components the Centers for Disease Control, the NIH, and the Food and Drug Administration--acted too slowly, with little coordination, and with meagre resources.

---

\*After Dinner Address Presented at the Howard Hughes Medical Institute Conference on Retroviruses and Immunosuppression, in Coconut Grove, Florida, October 28, 1985.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



I have always maintained that these charges are incorrect and unjustified. The NIH and the scientific community have been able to respond to AIDS in a remarkable way because of an enormous investment in fundamental research over the years. This fact, for the most part, is overlooked by our critics. By the time the first cases of AIDS were recognized in March and April of 1981-- incidentally by scientists at UCLA supported by the NIH--that prior investment in basic research had already generated a wealth of fundamental knowledge in such areas as immunoregulation, basic virology, opportunistic pathogens, the retroviruses, and DNA recombination. Without the benefit of these modern immunological understandings and technologies, it would have been impossible even to identify and characterize AIDS. In addition, a long standing national commitment to training research scientists--both M.D.'s and Ph.D.'s--assured the existence of a cadre of prepared researchers around the country who were ready to apply their expertise to the challenges posed by AIDS.

With these resources in place, along with a strong intramural research program, NIH was prepared to respond quickly. Scarcely four months after the syndrome was recognized, the first AIDS patient was admitted to the NIH Clinical Center. Very soon, nearly every NIH component became actively involved in the search for the causative agent, effective treatment, and a clearer explanation of the disease and all its facets. This collaborative effort involved, of course, the NIAID, the NCI, and the National Heart, Lung, and Blood Institute which have remained dominant in their involvement with AIDS, but also the National Eye Institute--

because of the ocular manifestations of AIDS; the National Institute of Neurological and Communicative Disorders and Stroke--because of their interest in the neurological consequences of certain viral diseases; and the National Institute of Dental Research--because of special expertise in that component with regard to certain viruses. The Division of Research Resources, which funds a number of Primate Research Centers around the country, has been involved in AIDS from the start because of the importance of animal models to this research. The NIH Clinical Center's role continues to be important--to date, more than 300 AIDS patients have been studied and treated there.

Early on, NIH included the extramural community in accelerated efforts. Supplemental awards were made by the NCI to scientists already supported by NIH so that their research focus could be redirected toward AIDS. This early effort to encourage research on AIDS by extramural investigators entailed diverting funds from other NIH programs because no money had been appropriated for AIDS research.

A number of workshops were held in an effort to bring together NIH researchers and scientists nationwide to discuss preliminary research leads and to develop a course of research action.

While the scientific community began to initiate studies on the causes of AIDS and some outstanding researchers turned their attention to the problem, the NCI developed and released a Request for Applications (an RFA) in August 1982. As a result of this

announcement 22 cooperative agreements were awarded. This was the first major effort to fund extramural research directly related to AIDS, and it was to be followed by about 15 similar solicitations to help stimulate research on AIDS.

Another early effort was aimed at educating the public and health care professionals about AIDS. Conferences sponsored by NIH were held around the country, aimed mainly at nurses, laboratory technicians, emergency medical personnel, and other service and support personnel who considered themselves to be at risk because of their occupations.

NIH also sought ways to expedite the peer review process for AIDS research applications. We recognized that, in general, there are trade-offs between speed and quality of review and determined that the need for quality was of overriding importance. Nonetheless, to hasten the award of new grants on AIDS, NIH set up special peer review panels and implemented a fast turn-around mail ballot system, accelerating the process by three or four months.

But the best evidence for the efficacy of a special effort, of course, is success. It is rather startling to review the testimony delivered by Dr. Edward Brandt, then Assistant Secretary for Health, before a Congressional committee on August 2, 1983. His testimony read, "Although we do not yet know the cause of AIDS, the evidence is strong that we are dealing with an infectious agent with a long incubation period . . . the most plausible agents are viruses . . . Unfortunately, it is not possible to predict when the cause of AIDS will be found." In May of 1983 a

team of French scientists, headed by Dr. Luc Montagnier, at the Pasteur Institute in Paris announced their discovery of LAV.

It was in May 1984 that Dr. Robert Gallo and his colleagues from the NCI published a series of papers in Science suggesting a particular retrovirus as the probable cause of AIDS and describing a key advancement: the ability to grow the HTLV-III in large amounts. These discoveries came just three years after the first clinical description of the disease itself--an accomplishment unusual in its rapidity, especially because the discovery of a wholly new agent was involved. This discovery has been termed "a mixture of intuitive brilliance and great good fortune,"<sup>1</sup> but it is also a tribute to the commitment made to biomedical sciences over the past twenty years.

More specifically, of course, this discovery arose from a background of information available about the human leukemia viruses--HTLV-I and HTLV-II--and was dependent upon expertise of the research team in working with these agents. The discovery of the AIDS virus in this way has been called an example par excellence of the wisdom of our investment in fundamental biomedical research.

Other advances followed rapidly. They included: a description of the underlying immune defects characteristic of the disease; the development of tests for screening donated blood; improved understanding of modes of transmission; development of methods for processing blood products used by hemophiliacs; complete deciphering of the genetic code of the causative virus;



and recognition that the brain is a primary site of infection. We have also learned a great deal about how the virus infects cells, about the antibodies produced by some people infected with the virus, and about the mechanisms by which the virus propagates. Many of these advances have laid important groundwork for our current challenges--development of therapeutic modalities and vaccines.

In terms of the budgetary response, funding for AIDS has expanded rapidly: in 1982, PHS allocated \$5.5 million for AIDS programs, with \$3.4 million for NIH; in 1984, the PHS total had climbed to \$61.5 million, with \$44.1 million for NIH. Estimates for 1985 are \$108.9 million for PHS as a whole and \$63.5 million for NIH.

It is interesting to note the change in the proportion of funds spent on AIDS intramurally and in extramural programs over the past four years--in 1982, 53 percent of the funds were spent on intramural AIDS programs and 47 percent extramurally; by 1985 the proportions had shifted so that only 25 percent of the much larger budget was allocated to intramural studies while 75 percent was spent for extramural projects. Some of our critics claimed early on that we were spending too large a proportion of the allocated money on intramural studies, but there were important reasons for this--first, NIH intramural scientists had a high level of expertise in viral research and in immune disorders, and second, disbursement of money in an emergency situation can be accomplished more quickly intramurally than through the granting

mechanisms. The change in the relative proportions--extramural to intramural--is seen as a natural evolution of the field of study.

Since the disease first appeared, there has also been concern raised by the Congress and various advocacy groups that the government's AIDS programs have been poorly coordinated and not strategically planned. This conception, I think, is more perceived than real, in part because the public does not understand, first, how scientists--given the same information or data--can have differing interpretations, and second, because the public does not comprehend how good, creative science is done. The disappointment with the government's effort against AIDS is also in part due to our early inability, as scientists and administrators, to explain the ways in which scientific knowledge is pursued and accrued.

In fact, the PHS efforts against AIDS are coordinated at various levels of the organization and have been since the disease was declared by the HHS Secretary as the Department's number one public health priority. Just to give you a summary of the organizational aspects of the AIDS effort--the PHS has a Plan for the Prevention and Control of AIDS, with which planning documents from the component agencies interdigitate. All of these plans, of course, are seen as flexible, with refinements being made continually as new insights and knowledge are gained through research.

The PHS Executive Task Force on AIDS, chaired by Dr. James Mason, Acting Assistant Secretary for Health, plays a continuing role in making important decisions concerning the efforts and

responsibilities of the PHS agencies in bringing the AIDS epidemic under control. For operational purposes, there are four specific task forces, including a Task Force on Vaccine Development and Therapeutic Interventions with members from FDA and CDC, which I chair, and a Task Force on Epidemiology and Prevention, chaired by Dr. Mason. Two other task forces relate to blood and blood products, and to the psychological and psychiatric aspects of AIDS. At the NIH level, we similarly have in place an Executive Task Force with wide NIH representation.

We cannot expect, however, that criticism of the government's response to AIDS will cease. Such criticism tends to die down for a period of time, only to well up again on a slightly different note. For example, although public interest in AIDS itself has remained high--particularly the aspect of heterosexual transmission--public interest in AIDS research was at an ebb until the media reported that Rock Hudson had traveled to Paris for treatment for AIDS. Early media coverage of this episode left the impression in the minds of the public--and the Congress--that little was being done in this country to develop means of treating AIDS. In fact, we had already screened more than 100 agents for potential as AIDS treatments and already were clinically testing about six promising drugs. NIH had deliberately avoided public attention for these efforts because of the preliminary nature of the studies and because of our determination not to appear to be over-promising. As a result, the scope of our treatment development efforts did not become known until Congressional hearings this July.

I would predict that the next wave of negative public sentiment will arise over vaccine development, because I do not believe that we have made clear to the media, the general public, and the Congress the technical and clinical difficulties that attend this effort, and subsequently the long time frame we face. It is impossible for the government to escape criticism in our long-term efforts to combat AIDS--given the nature of the disease and the way in which science is conducted, and given the roles the Congress, the advocacy groups, and the media typically play in public policy issues of this sort.

At this point, permit me to provide you with an overview of NIH research plans for FY 1986.

In FY 1986, NIH will capitalize on the extensive research advances already made on AIDS-related disorders, principally through epidemiologic studies to clarify the natural history of the disease and through initial work toward the development of vaccines and treatment modalities.

NIH will continue to support basic research involving antigenic viral components, stressing antigens that are common to many virus strains and that would elicit neutralizing and/or protective antibodies. Additional studies are needed on latency; incorporation of the viral genome in the host cell and activating factors; inhibition of viral growth; isolation of the virus from various body fluids; identification of markers for predicting the occurrence of clinical disease in virus-exposed individuals; development of diagnostic tests and viral isolation; and the



determination of genetic and other variations among HTLV-III isolates.

A wide range of epidemiologic research on AIDS is being conducted at NIH, by its grantees and in collaboration with other agencies of the PHS. The objectives of these studies are to develop an understanding of how infection occurs, how frequently and under what circumstances HTLV-III infection persists in infected individuals, and which infected individuals are most likely to transmit HTLV-III. Such studies should also help elucidate the severity of disease in relation to time and source of infection, risk factors, time frames for the development of antibodies to HTLV-III, and the role of host factors and cofactors in disease risk. To cite some examples:

- o The National Institute of Allergy and Infectious Diseases (NIAID) is supporting a large multi-center study of the natural history of AIDS in homosexual men. Specifically, 5,000 homosexual men in Baltimore, San Francisco, Chicago, Los Angeles, and Pittsburgh are being followed longitudinally for three years. The objective is to resolve issues concerning the clinical spectrum of HTLV-III infections, the implications of a positive serologic test for an individual, the prevalence of circulating and/or shed virus in antibody-positive persons, and the prognosis for seropositive individuals with mild or no signs of disease. A similar group of men from New York also will be evaluated. While this study was originally set up to collect specimens in an

attempt to determine the etiologic agent of AIDS, it has been converted into a natural history study. Biological specimens collected from each of these populations will be made available to intramural and extramural scientists for study.

- o We are also supporting a large study of the natural history of HTLV-III infection in newborns. This involves the identification of HTLV-III positive pregnant women, spouses of patients, parenteral drug users, and Haitians, and the subsequent laboratory and clinical evaluation of their offspring up to two years of age.
- o A study is being made of HTLV-III transmission in seropositive, pregnant, drug-using females and their offspring, with followup of the children to monitor seroconversion, immune function, and risk of AIDS.
- o In another study, investigators will evaluate the immune function of individuals at high risk for AIDS for at least two years to determine whether any of them develop AIDS symptoms. Attempts will be made to identify immune abnormalities that may be predictive for AIDS and could help elucidate the mechanisms leading to disease.
- o Further studies are needed on AIDS encephalopathy and the substantial data indicating that the retrovirus HTLV-III is present in the brain of AIDS patients. It is of clinical, therapeutic, and epidemiological importance to

determine what percentage of currently seropositive individuals may harbor HTLV-III in their brains.

Scientists at NIH and elsewhere working on drugs to combat AIDS are focusing in two directions simultaneously: first, on the development of antiviral agents to inhibit the replication of HTLV-III; and second, on the development of a means to reconstitute the failing immune system. It is likely that AIDS patients must be treated with at least two agents concomitantly, an antiviral agent and an immune enhancer, in order successfully to combat the disease.

Efforts are also under way to improve means of treating the opportunistic infections--such as Pneumocystis carinii pneumonia, viral infections, and the cancers that commonly afflict patients with AIDS. Separate attention is being given to the development of treatments for children with AIDS because information on drug effects and metabolism derived from studies in adults may not be applicable to children.

While no effective treatment yet exists to destroy permanently HTLV-III residing in AIDS patients and fully and permanently to reconstitute the immune system, a host of promising new remedies are under investigation at NIH and elsewhere. These could, within the next few years, make a major difference to people with the disease. Regarding the "secondary" or opportunistic diseases that strike AIDS patients, there have been some notable advances. For example, clinical studies on the drug DHPG have shown dramatic results in AIDS patients with vision-

threatening retinitis and other problems--such as debilitating colitis--caused by cytomegalovirus (CMV). This is especially important because CMV infections cause significant morbidity and mortality in AIDS patients and because in the past no drug has been effective against CMV.

To hasten as much as possible the development of promising new compounds for treatment of AIDS patients, NIH has formalized a plan involving NIAID, the NCI, the extramural research community, and the FDA. This program spans research activities from drug screening and discovery, through preclinical testing to clinical testing.

To date, more than 100 candidate compounds have been selected and passed through an NCI-developed assay and screened for their antiviral qualities. Several of these drugs are now being tested in AIDS patients.

Currently, the NIAID and NCI scientists are testing or are about to test seven drugs, either alone or in combination, in AIDS patients at the NIH Clinical Center. The drugs include: suramin, ribavirin, foscarnet (phosphonoformate), alpha interferon, interleukin-2, HPA-23, and a compound designated A509U. In addition, NIH scientists are investigating the role of bone marrow transplants to replenish the immune system in three patients with AIDS, each of whom has an identical twin to provide for the transplant.

Through its extramural programs, NIH is expanding drug discovery and testing efforts to centers across the country,



particularly in areas where AIDS is most prevalent. For example, clinical testing of various drugs is going on in several NIH-supported General Clinical Research Centers; and the NCI, in conjunction with NIAID, is testing suramin--a promising antiviral--at six centers arounds the country. This cooperative study will initially involve approximately 150-200 patients with expansion possible depending upon results. Additionally, in September, the NCI and NIAID issued a joint solicitation to research centers around the country for the establishment of AIDS Treatment Evaluation Units. Studies at these units will involve testing of antivirals, immune modulators, and antibiotics in patients with subclinical and clinical HTLV-III infections.

NIH is working closely with agencies throughout the PHS in developing improved methods for control of AIDS. The principal objective of NIH efforts in prevention is to develop and evaluate new approaches for detecting infection as well as to develop passive and active immuno-prophylaxis. Efforts are aimed at developing better methods to detect AIDS antibody and at devising simple, rapid, and sensitive methods to detect and isolate HTLV-III. A great many approaches are being made to vaccine production. These include extracting candidate antigens from large-scale production of virus; identifying appropriate antigens and synthesizing them; inserting appropriate genomes into bacteria or yeast for antigen production; inserting appropriate HTLV-III genome segments into vector viruses; and synthesizing peptides of the viral envelope products.

Another emphasis is on development of animal models of AIDS in which candidate drugs and vaccines can be tested. Studies are continuing on naturally occurring animal retrovirus infections that stimulate AIDS--such as Simian AIDS.

Studies are also being done on the transmission of HTLV-III from humans to nonhuman primates. These projects will attempt to establish a reproducible means to induce clinical manifestations of AIDS in nonhuman primates, in order to develop a better animal model for the disease. Such a model promises to provide investigators with ways to assess the natural history of AIDS and evaluate a variety of interventive measures for the treatment or prophylaxis of human AIDS. Another aspect of these studies will be to mate infected or seropositive animals and study their offspring to further investigate maternal-fetal transmission of HTLV-III. Additionally, serial passage of HTLV-III will be made in chimpanzees, paralleling comparable studies of natural infections in man, to determine if antigenic drift occurs, an important factor in vaccine development.

The final appropriation for AIDS for Fiscal Year 1986 remains unsettled at present. The amended President's Budget includes approximately \$71 million for AIDS research supported and conducted by the NIH. The House allowance provides for an additional \$70 million, and the Senate Appropriations Committee has provided an increase of \$57 million. Differences in the recommended funding levels will be resolved in a House-Senate Conference. While we do not know at this point precisely how much money will be allocated to continued AIDS research, it seems

that it will be a substantial amount, most of which will be spent for extramural research projects.

<sup>1</sup> Testimony of Dr. William A. Haseltine, Chief, Laboratory of Biochemical Pharmacology, Dana-Farber Cancer Institute, Harvard Medical School, before the Labor-HHS-Education Subcommittee, September 26, 1985.

STATEMENT BY

JAMES B. WYNGAARDEN, M.D.  
DIRECTOR  
NATIONAL INSTITUTES OF HEALTH  
PUBLIC HEALTH SERVICE  
DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON  
SCIENCE, RESEARCH, AND TECHNOLOGY  
OF THE  
COMMITTEE ON SCIENCE AND TECHNOLOGY  
U.S. HOUSE OF REPRESENTATIVES

October 30, 1985



MR. CHAIRMAN AND MEMBERS OF THE SUBCOMMITTEE:

I AM PLEASED TO BE HERE TODAY TO SHARE WITH YOU MY VIEWS ON THE STATE OF OUR UNIVERSITY RESEARCH FACILITIES. AN ASSESSMENT OF THE CONDITION OF THESE FACILITIES AND THE EXTENT OF THE NEED FOR THEIR REPLACEMENT AND RENOVATION HAS BEEN THE SUBJECT OF CONSIDERABLE DISCUSSION, AND RECENT STUDIES HAVE RAISED QUESTIONS ABOUT THEIR ADEQUACY. FEDERAL AGENCIES HAVE RECEIVED MANY EXPRESSIONS OF CONCERN THAT DETERIORATING RESEARCH FACILITIES HAVE BECOME A SERIOUS PROBLEM FOR ACADEMIC SCIENTISTS AND ENGINEERS, MATERIALLY AFFECTING THEIR ABILITY TO WORK COMPETITIVELY AT THE FRONTIERS OF SCIENTIFIC AND ENGINEERING KNOWLEDGE. IN APRIL 1984, AN AD HOC INTERAGENCY STEERING COMMITTEE COMPRISING THE DOD, NIH, DOE, USDA, AND NSF OBTAINED 5-YEAR CONSTRUCTION PLANS FROM 25 INSTITUTIONS. ON THE BASIS OF THESE PLANS, THE LEVEL OF POTENTIAL EXPENDITURE WAS ESTIMATED. ALTHOUGH LIMITED IN SCOPE, THE EFFORT PROVIDES US WITH A SENSE OF THE CONSTRUCTION PLANS OF SOME OF OUR UNIVERSITIES.

THERE IS LITTLE DOUBT THAT INVESTMENT IN THE RESEARCH FACILITIES OF OUR UNIVERSITIES HAS BEEN LONG DEFERRED AND DEMANDS ATTENTION IF WE ARE TO PRESERVE OUR PREEMINENCE IN SCIENCE. THE PROPOSED BILL, H.R. 2823, SEEKS TO MANDATE THIS INVESTMENT. WE CONCUR WITH THE INTENT OF THE BILL. WE DO NOT FAVOR THE MECHANISMS WITHIN THIS BILL AND CANNOT SUPPORT IT IN ITS PRESENT FORM.

BEGINNING IN 1956, THERE WAS A GREAT DEAL OF LEGISLATION ADDRESSED TO THE RESEARCH FACILITY NEEDS OF THE NATION. THE HEALTH RESEARCH FACILITIES ACT OF 1956 (P.L. 84-835) WAS ONE SUCH MEASURE. DURING ITS 14-YEAR LIFESPAN, \$484 MILLION IN MATCHING FUNDS WAS OBLIGATED BY THE NATIONAL INSTITUTES OF HEALTH FOR RESEARCH FACILITIES CONSTRUCTION. AFTER 1968, NO FURTHER FUNDS WERE APPROPRIATED FOR THIS AUTHORITY, WHICH SUBSEQUENTLY EXPIRED WITH ITS REPEAL IN 1974. THIS LEFT A VACUUM, ONLY PARTIALLY FILLED BY CONSTRUCTION AUTHORITIES CARRIED AS PARTS OF OTHER LEGISLATION, SUCH AS: THE NATIONAL CANCER ACT OF 1971 (P.L. 92-218); THE NATIONAL HEART ACT OF 1948 (P.L. 80-655); THE NATIONAL HEART, BLOOD VESSEL, LUNG, AND BLOOD ACT OF 1972 (P.L. 92-423); AND THE HEALTH SERVICES RESEARCH, HEALTH STATISTICS, AND HEALTH CARE TECHNOLOGY ACT OF 1978 (P.L. 95-623), THE LATTER PROVIDING CONSTRUCTION AUTHORITY FOR THE NATIONAL EYE INSTITUTE.

UNDER THE NATIONAL CANCER ACT AUTHORITY, BEGINNING IN 1971 AND STILL IN EFFECT, SOME \$289 MILLION IN MATCHING FUNDS HAS BEEN OBLIGATED FOR CONSTRUCTION THROUGH 1985. SINCE 1968, \$3.3 MILLION HAS BEEN OBLIGATED FOR CONSTRUCTION BY THE NATIONAL HEART, LUNG, AND BLOOD INSTITUTE. UNDER A SPECIFIC AUTHORITY PROVIDED FOR THE NATIONAL EYE INSTITUTE FOR "A PROGRAM OF GRANTS FOR PUBLIC AND NONPROFIT PRIVATE VISION RESEARCH FACILITIES" IN FY 1979 AND STILL IN EFFECT, FUNDS WERE OBLIGATED IN FY 1982 IN THE AMOUNT OF \$5 MILLION AND IN FY 1985 IN THE AMOUNT OF \$3.3 MILLION. ALL OF THESE OBLIGATIONS WERE IN THE FORM OF GRANTS TO BE MATCHED WITH A LIKE AMOUNT OF NON-FEDERAL FUNDS. FINALLY, AND OFTEN NOT INCLUDED IN ASSESSMENTS OF

FEDERAL CONTRIBUTIONS TO UNIVERSITIES' FACILITIES NEEDS, THE NIH PROVIDES AN ESTIMATED \$70 MILLION PER YEAR IN USE ALLOWANCES AND DEPRECIATION COSTS TO THE UNIVERSITIES. THESE AMOUNTS ARE INCLUDED IN INDIRECT COST PAYMENTS ASSOCIATED WITH EACH GRANT.

THE NATIONAL INSTITUTES OF HEALTH FULLY REALIZES AND SUPPORTS THE NEED TO ASSESS THE REQUIREMENTS OF UNIVERSITY RESEARCH FACILITIES BEFORE MASSIVE RESOURCES ARE COMMITTED FOR CONSTRUCTION AND RENOVATION. RESEARCH UNIVERSITIES HAVE DIFFERENT EXPENSES AND NEEDS ACCORDING TO THEIR AGE, LOCATION, AND AREAS OF DISCIPLINARY EXPERTISE. THE RESEARCH POTENTIAL OF EACH INSTITUTION IS DEPENDENT ON THE CONDITION OF ITS RESEARCH INFRASTRUCTURE, THAT IS, PEOPLE, EQUIPMENT AND FACILITIES. WE ARE KEENLY AWARE THAT TODAY'S SCIENTIFIC INVESTIGATION IS NEXT TO IMPOSSIBLE WITHOUT STATE-OF-THE-ART FACILITIES AND INSTRUMENTATION.

THE REALISTIC AIM OF ANY ADDITIONAL CONSTRUCTION AUTHORITY SHOULD BE TO COMPLEMENT THE EXISTING AUTHORITIES. TO ENSURE THAT ANY NEW OR ADDITIONAL PROGRAM ENHANCES THE STABILITY, CONTINUITY, AND SUSTAINED LONG-TERM EFFECTS OF THE PRESENT PROGRAMS, ADDITIONAL DATA ARE NEEDED. IT SHOULD ALSO BE POINTED OUT THAT ANY EFFORT TO ADDRESS THE PROBLEM OF UNIVERSITY RESEARCH FACILITIES SHOULD EMPHASIZE THE PARTNERSHIP BETWEEN THE FEDERAL AND LOCAL GOVERNMENTS, THE UNIVERSITIES, AND THE PRIVATE SECTOR.

THERE APPEARS TO BE A GROWING CONSENSUS THAT A PROBLEM EXISTS WITH RESPECT TO FACILITIES' OBSOLESCENCE. THUS, WHILE I SUPPORT THE GENERAL INTENT OF THE PROPOSED LEGISLATION, I HAVE SERIOUS RESERVATIONS ABOUT THE APPROACH. OUR SPECIFIC CONCERNS WITH THE BILL ARE THESE: (1) THE 10 PERCENT SET-ASIDE AFTER THE INITIAL YEAR FOR WHICH FUNDING IS PROVIDED; (2) THE LIMITATION THAT SUCH A SET-ASIDE WOULD HAVE ON THE FLEXIBILITY TO ADMINISTER THE OVERALL RESEARCH PROGRAM; (3) THE FACT THAT AVAILABILITY OF THESE FUNDS IS LIMITED TO UNIVERSITIES AND COLLEGES; (4) THE OVERLAP OF AUTHORITY PROVIDED BY THE BILL WITH OTHER EXISTING CONSTRUCTION AUTHORITIES; (5) THE COSTS OF ADMINISTERING THE PROGRAM; AND (6) THE REPORTING FREQUENCY SPECIFIED IN THE BILL.

(1) THE LANGUAGE OF THE BILL MAKES NO PROVISION FOR ANY NEW FUNDING AFTER THE INITIAL YEAR, FY 1987, WHEN "START-UP" FUNDS IN THE AMOUNT OF \$470 MILLION (THE DHHS PORTION IS \$200 MILLION) ARE AUTHORIZED TO BE APPROPRIATED. FOR THE OUT YEARS, FY 1988 THROUGH FY 1996, FUNDING FOR THE PROGRAM WOULD BE INCORPORATED INTO THE RESEARCH BASE AS PART OF THE AGENCIES' REGULAR ANNUAL APPROPRIATIONS. EVEN THOUGH PROVISIONS ARE MADE FOR REDUCING THE SET-ASIDE SHOULD THE APPROPRIATION BE REDUCED--REDUCING IT TO ZERO SHOULD THE APPROPRIATION BE REDUCED BY 10 PERCENT OR MORE--WE HAVE GRAVE CONCERNS ABOUT THE EFFECT THE SET-ASIDE MIGHT HAVE ON OTHER EXTRAMURAL RESEARCH PROGRAMS.

(2) RESERVATION OF FUNDS ON A FIXED PERCENTAGE BASIS WOULD LIMIT



ADMINISTRATIVE FLEXIBILITY. ALTHOUGH A FIXED ALLOCATION IS A POTENTIALLY EFFECTIVE WAY TO MONITOR EFFECT AND COMPLIANCE, IT COULD, IN THE LONG RUN, BE DETRIMENTAL BY DENYING THE AGENCIES FLEXIBILITY IN DETERMINING THE AMOUNTS TO BE RESERVED IN ANY PARTICULAR PERIOD.

(3) THE LANGUAGE OF THE BILL LIMITS FACILITIES MODERNIZATION TO UNIVERSITIES AND COLLEGES. THIS IMPACTS ONLY A SEGMENT, ALBEIT A LARGE AND IMPORTANT ONE, OF THE NOT-FOR-PROFIT INSTITUTIONS THAT PERFORM RESEARCH. IN 1984, 75 PERCENT OF NIH EXTRAMURAL FUNDS WENT TO COLLEGES AND UNIVERSITIES, BUT 19 PERCENT WENT TO OTHER NONPROFIT INSTITUTIONS, SUCH AS INDEPENDENT HOSPITALS AND RESEARCH INSTITUTES, WHICH ARE MAJOR CONTRIBUTORS TO OUR NATION'S RESEARCH EFFORT. NO PROVISION HAS BEEN MADE FOR THE ELIGIBILITY OF THESE ORGANIZATIONS AND THEY ARE NO LESS WANTING WITH RESPECT TO FACILITIES RENOVATION. IN FACT, OUR CURRENT SYSTEM OF FUNDING THROUGH THE INDIRECT COST MECHANISM DOES NOT DISCRIMINATE AGAINST THESE INDEPENDENT RESEARCH ORGANIZATIONS.

(4) THERE IS CONCERN WITH THE MATTER OF OVERLAP WITH OTHER CONSTRUCTION AUTHORITIES CURRENTLY IN EFFECT. THESE INCLUDE:

(a) THE NATIONAL CANCER ACT OF 1971 (P.L. 92-218), WHICH PROVIDES AUTHORITY FOR THE NCI TO MAKE CONSTRUCTION GRANTS.

(b) THE NATIONAL HEART ACT OF 1948 (PUBLIC LAW 80-655), WHICH AUTHORIZED THE EXPENDITURE OF FUNDS FOR GRANTS FOR THE CONSTRUCTION OF FACILITIES FOR

RESEARCH RELATED TO HEART DISEASES; AND THE NATIONAL HEART, BLOOD VESSEL, LUNG AND BLOOD ACT OF 1972 (PUBLIC LAW 94-423), WHICH AUTHORIZED THE EXPENDITURE OF FUNDS FOR THE CONSTRUCTION OF NATIONAL RESEARCH AND DEMONSTRATION CENTERS FOR HEART, BLOOD VESSEL, LUNG, AND BLOOD DISEASES.

(c) THE HEALTH SERVICES RESEARCH, HEALTH STATISTICS, AND HEALTH CARE TECHNOLOGY ACT OF 1978 (P.L. 95-623), WHICH AMENDED THE PUBLIC HEALTH SERVICE ACT "TO CARRY OUT A PROGRAM OF GRANTS FOR PUBLIC AND NONPROFIT PRIVATE VISION RESEARCH FACILITIES."

(5) THERE IS CONCERN ABOUT THE ADDITIONAL COSTS REQUIRED TO ADMINISTER AND CARRY OUT THE OBJECTIVES OF THE PROGRAM (TO CONDUCT REVIEWS, SITE VISITS, GRANTS MANAGEMENT, ETC.). DURING A PERIOD OF CONTINUING BUDGET AND MANPOWER CONSTRAINTS, THIS COULD PROVE TO BE A PARTICULARLY VEXING PROBLEM.

(6) COROLLARY TO THE THE ABOVE IS THE FREQUENCY OF REPORTING ON THE IMPLEMENTATION AND THE EFFECT OF THE BILL. REPORTS ARE REQUIRED TO BE SUBMITTED TO THE CONGRESS EVERY TWO YEARS. THOUGH THE NATIONAL SCIENCE FOUNDATION BEARS THE BRUNT OF THIS RESPONSIBILITY, IT WOULD BE CARRIED OUT IN CONJUNCTION WITH THE OTHER FEDERAL AGENCIES. IT WOULD BE PREFERABLE THAT THIS BE DONE ON A 5-YEAR BASIS, OR ON AN ALTERNATING CYCLE OVER SEVERAL YEARS AND INSTITUTIONS.

I WOULD BE HAPPY TO RESPOND TO ANY QUESTIONS THE SUBCOMMITTEE MAY HAVE.



"PROGRESS AND PROMISE IN DIABETES RESEARCH"\*

BY

James B. Wyngaarden, M.D.\*\*

It is a privilege and pleasure to attend and participate in this truly remarkable conference. The Juvenile Diabetes Foundation International (JDFI) has exercised imagination and initiative in planning for their symposium and has gone about conducting it with the energy and ability we have come to associate with JDFI. All of us who are concerned about diabetes are grateful for the impressive financial support that has made this conference possible.

I will take advantage of my place on the program as keynote speaker to address some of the gains that have been made in the fight against diabetes and identify some of the promising new strategies to be employed in that effort. In the rich days to follow you will hear these and other important subjects discussed in depth by world known experts.

Two fundamental puzzles underlie contemporary diabetes research. The first and most compelling is the mystery of what causes the disease. An answer to this question is essential to developing a means of preventing and curing diabetes.

Also a mystery, and a critical one in the current absence of a cure, is why diabetes, even when treated, causes such devastating long-term complications. Complications are the major cause of death and disability in diabetes. If complications posed no risk, the impact of the disease would be greatly reduced. Insulin would provide a much more satisfactory remedy to diabetes than it has.

In the ten years since the National Commission on Diabetes met to formulate a long-range plan to combat diabetes, progress toward answering these two questions has been enormous. Two key sets of circumstances--one legislative and the other scientific--coupled to make this major and continuing wave of progress possible. The National Diabetes Mellitus Research and Education Act of 1974 greatly increased the focus on diabetes as a national health priority. The resources available to conduct research on this disease multiplied in the wake of the Act and the report of the National Commission.

---

\*Keynote address at the Juvenile Diabetes Foundation International World Conference on Diabetes Research in Monaco, November 4, 1985

\*\*Director, National Institutes of Health, Bethesda, Maryland



As an illustration, in Fiscal Year 1975, NIH-wide funding of diabetes-related research was \$39 million. In Fiscal Year 1985, this funding had increased to \$204 million.

Even this increased focus on--and dollars devoted to--diabetes would not have brought the progress it has if a second and equally important set of circumstances had not been right. This new focus came at a time at which ongoing scientific research had laid a broadening foundation of basic understanding of physiology, genetics, and immunology. The tools needed to attack the questions posed by diabetes were there. In the last decade, scientists in the diabetes field have capitalized to the fullest on these resources. As a result, the growth in recent years of our understanding of diabetes has been unprecedented. While the primary goal--a cure for diabetes--awaits discovery, this progress has been heartening and has further fueled the pace of research.

Compare, for example, the framework of our current understanding of the genetics of diabetes with our understanding 10 years ago. In the 1970's, we knew that there was a distinct difference in the role of heredity in noninsulin-dependent and insulin-dependent diabetes. The monozygotic twin of a person with NIDDM was almost certain to have NIDDM. On the other hand, the monozygotic twin of a person with IDDM had only about a 50 percent chance of also developing the disease.

The identification in the mid-1970's that people with IDDM are more likely than the population as a whole to have particular HLA antigens was a major step on the way to understanding inheritance as a risk factor in IDDM. Many investigators have confirmed the strong association between insulin-dependent diabetes and HLA-DR3 and DR4. We do not know yet the exact role these alleles play in the cause of diabetes, but genetic and immunologic technology is continuing to provide the tools with which we will answer this question. It appears, for example, that molecular cloning of the products of histocompatibility antigens will tell us more about these genes and their products than serologic testing for the antigens can. This technology will be the key to determining whether these HLA alleles themselves convey susceptibility to diabetes, or whether they are located close to a diabetes gene or genes on the chromosome.

Genetic research on diabetes has progressed in tandem with advances in our understanding of the immunology of IDDM. It is clear that in IDDM the destruction of islet cells is an immunologic process. Further research on the role of HLA alleles in determining the internal immunologic "climate" of an organism is critical to understanding how IDDM occurs. At the same time, immunologic research has done much to characterize the immune processes active in IDDM. We know that both cell-mediated and humoral immunity play a role in islet-cell destruction. Continuing application of immunologic technology, notably the use of monoclonal antibodies, promises to provide a means of characterizing the antigenic determinants in pancreas tissue that may have a role in the autoimmune process.

Many questions remain with regard to the cause of insulin-dependent diabetes. With the sophisticated tools now available to us, however, we are able to address this question with a versatility that would be otherwise impossible. Furthermore, this research is already pointing the way to

possible means of early identification of susceptibility to diabetes and of early intervention. The ability to detect islet-cell antibodies has provided a means to screen risk groups--namely, first-degree relatives of persons with insulin-dependent diabetes--for the presence of the antibodies as a possible indicator of incipient diabetes. As you have all read recently, results from George Eisenbarth's group at the Joslin Clinic indicate ICA screening has potential as an early warning of diabetes. Clinical trials are already looking at the possibility that immune suppression may be an avenue of intervening early in diabetes and preventing progression of the autoimmune process to frank insulin-dependent diabetes.

Genetic and immunologic research promises to shed light not only on the underlying causes of diabetes, but on the clinical variability of the disease. However, an understanding of the causes of diabetes cannot be complete without knowledge of the mechanism of insulin action and the other hormones that play a role in glucose homeostasis. Already we are beginning to shape a picture of the complexity of this process. Each step in the sequence of glucose control offers another corner in which to search for a defect that might impair glucose metabolism and that might offer an avenue of intervention.

A milestone in diabetes research was achieved earlier this year by two independent groups of researchers who cloned the insulin receptor gene and derived the insulin receptor protein sequence. This discovery opens the door to further research to clarify the synthesis of the receptor, its orientation on the cell surface, how it interacts with insulin, and how it acts to promote intracellular processing of glucose.

Sequencing of the insulin receptor is an eagerly awaited tool for scientists who have been attempting to characterize the mechanisms of insulin action at the cellular level, after hormone-receptor coupling. Important groundwork has already been laid in this area. Out of this work has come the description of an ever greater number of the component steps in insulin's effect on glucose transport and metabolism, and the molecular and enzymatic processes by which insulin effects these changes.

For example, continuing research has explored the identification of putative second messengers of insulin. Receptor binding may release an as yet uncharacterized intermediary molecule that acts on several insulin-sensitive enzymes. Characterization of such a molecule is an important goal of ongoing studies.

Characterization of a second messenger will be a key to further elucidation of how insulin acts to control glucose homeostasis. We have already described a number of insulin's effects at the cellular level. We know, for example, that insulin-stimulated glucose transport is associated with an increase in recruitment of glucose transporters from the interior of the cell to the cell surface.

Molecular genetic techniques have made possible the demonstration that insulin inhibits transcription of the gene for PEPCK, the rate-limiting enzyme in the gluconeogenic pathway.

Insulin modulates the activities of a number of enzymes that control glucose homeostasis. We now know that the activities of many of these enzymes



are themselves modulated by phosphorylative processes. Research is bringing us closer to characterization of how insulin and glucagon can influence glucose metabolism through control of phosphorylation or dephosphorylation of these enzymes.

The insulin receptor itself is phosphorylated in response to binding with insulin. The receptor in this case both stimulates and is the substrate for phosphorylation. The availability of the insulin receptor structure will be of particular value in studying this phenomenon. Research has demonstrated that one of the first steps in insulin action after insulin binds with the receptor is the phosphorylation of tyrosine residues in the receptor. Continuing studies will clarify whether receptor phosphorylation is a necessary step in the sequence of insulin action on glucose metabolism and, if so, how phosphorylation influences the activities of many enzymes involved in insulin-mediated glucose metabolism.

Insulin is not the only hormone that plays a role in glucose homeostasis. Research on the variety of other hormones that regulate day-to-day glucose level can both complete our understanding of these processes and provide new avenues of treatment. Hypoglycemia, for example, is a special hazard in insulin-dependent diabetes. Research clarifying the role of hormones such as epinephrine and glucagon in the origin and the warning symptoms of hypoglycemia may help prevent this serious complication. Recently, growth hormone was implicated in the etiology of the dawn phenomenon, an early morning rise in blood glucose levels.

At a more fundamental level, important work is being done on the interrelationships and cross-reactivity of various insulin-like growth factors with their respective receptors. This research lays the foundation for an understanding of the coordination of control of growth and metabolism by the multiple hormones that now appear to have a role in these processes.

Clearly, progress towards the complete description of the cause and the mechanisms of diabetes has been tremendous. At the same time, research has rightly continued on the mechanisms and treatment of the complications of diabetes, the cause of most of the disability and death associated with this disease. Especially puzzling is why some individuals with diabetes have so much trouble with complications, while others seem to do relatively well over the course of years. With the fruits of recent research, we are beginning to have the means to answer these questions.

Notable among the investigations on the cause of diabetic complications has been the description of the role of aldose reductase in the development of diabetic cataracts. This research has led to the evaluation of aldose reductase inhibitors and ongoing clinical studies of the effectiveness of such agents in the prevention not only of diabetic eye disease, but other diabetic complications as well.

Another recent advance that could have important implications for understanding the microvascular complications of diabetes was the sequencing of a protein--and the corresponding gene--for what has been named angiogenin, a potent stimulator of blood vessel growth. While this advance has been widely reported as having important implications in cancer research, it could also provide a key in the search for the cause of proliferative vascular

disease in diabetes. It will provide a starting point for the design of agents that can inhibit angiogenin and vascular proliferation such as that seen in diabetes.

In the realm of treatment, research has provided new options and new hope for the individual at risk for the most serious diabetic complications. Examples include laser photocoagulation and vitrectomy for diabetic retinopathy and transplantation for diabetic renal disease.

The diabetes community can take great pride and satisfaction in the scientific advances it has achieved in the past decade. I have only sketched an outline of the approaches this work has taken. Many experts at this meeting will be providing a more complete picture of their ongoing work. The achievements I have described, and many I have not been able to touch on, will be the basis for the discovery of a means of prevention and cure of diabetes.

In the more immediate future, I think we will see advances that will greatly enhance our ability to treat this disease until a cure is found. The insulin pump, new forms of purified insulin, and home blood glucose monitoring are examples of the new options we have in treating diabetes. Tests for glycosylated hemoglobin offer a means of obtaining an integrated index over time of glucose levels and thus of diabetic control.

All of this technology now permits greater and greater ability to control blood glucose levels. Greater control cannot be achieved without a substantial commitment of time and effort both on the part of the health care practitioner and especially a person with diabetes. Maintaining close to normal blood glucose levels is not without hazard. This new technology not only permits us a new treatment capability, but offers the means to test the clinical impression that the better the glucose control, the lower the risk complications. Without a diabetes cure, this remains a crucial question in diabetes treatment, and it is being addressed now by the NIH-sponsored Diabetes Control and Complications Trial or DCCT. Just this fall, the DCCT successfully completed a 2-year feasibility stage. Its centers will now undertake full-scale recruitment of the total 1400 volunteers required to answer this therapeutic question. The results of the trial will have wide-reaching impact on the treatment of persons with insulin-dependent diabetes.

Tight control has already proven of clear benefit in situations such as diabetic pregnancy. Normalizing blood glucose in the course of pregnancy has been shown to enable a reduction in risk of perinatal mortality to that seen in pregnancies uncomplicated by diabetes. Birth defects, however, remain more common among infants of diabetic mothers than in infants of mothers without diabetes. Continuing research has demonstrated that the birth defects likely to be seen in diabetes occur in the first weeks of pregnancy, before the mother is aware she is pregnant. Clinical trials are now beginning to look at the effectiveness of initiating tight control of diabetes in mothers who are planning to become pregnant. If, as we hope, good control can indeed reduce the risk of birth defects, diabetes will be much less of a source of concern to women who are contemplating childbearing.

Research also promises to furnish new means of normalizing blood glucose in individuals with diabetes. Research continues to increase the versatility and applicability of insulin pumps. Implantable pumps have also been designed



and in some cases tested clinically. The design of an implantable device that can replace the complex endocrine functions of the pancreas, however, is a formidable task. Another approach, transplantation of donor pancreas cells to replace those lost in diabetes, is progressing with exciting rapidity. Within the last year, there has been a resumption of human islet transplantation that has been made possible by the development of new techniques for preparation of tissue.

Transplantation of pancreas tissue offers great hope for providing recipients with a close facsimile of the normal function of the pancreas. Especially exciting is the possibility that with pretreatment, islet cells might be transplanted without the need for accompanying immunosuppression. Obstacles remain, but I think this line of research is one that will be watched closely by the diabetes community.

Advances in pancreas and islet cell transplantation have, like the other advances in diabetes research, depended upon technical capabilities developed in other scientific fields. Immunologic research, new means of isolating and treating pancreas tissue, drugs such as cyclosporine, have all had an impact on diabetes research and treatment. Equally important has been the availability of scarce and often difficult to obtain resources needed for scientific research. One example is the need for a variety of human and animal tissues. These are needed to establish cell lines that are critical to studies and manipulations in vitro. In this regard, I would like to emphasize the value of efforts like the National Diabetes Research Interchange (NDRI). Faced with the stated need by researchers for various tissues that could be obtained in a timely manner and adequately preserved, the JDF established the interchange to serve as a resource for the collection and distribution of human tissues to be used in research. It is proving an invaluable asset to the diabetes research effort. With the support of both private organizations and the government, it also provides an example of what private and public sector collaboration can accomplish at a time when every research dollar is precious. Transplantation research has clearly been a beneficiary of the NDRI's unique service. Tissues will remain a critical need in any number of areas of diabetes research--transplantation, immunology, genetics, pharmacology, and so on. The NDRI can serve as a model for this type of joint initiative and its value to research.

If the future of diabetes research follows in the pattern of its recent history, we can look forward to a fascinating decade and one that will provide hope as never before that diabetes need not mean a life of vigilance for continued good health. For basic research, the two major questions that face current research--the cause of diabetes and the mechanism of complications--will remain the focus of ongoing work. The groundwork laid for these investigations in recent years is impressive. I believe we can look forward to important discoveries in the not too distant future related to the determinants, environmental and genetic, that set on course the immunologic destruction of insulin-producing cells seen in IDDM. With continuing applications of the growing arsenal of immunologic techniques, we should come to an understanding of the mechanism of autoimmune tissue destruction, not only in diabetes, but in other diseases in which this process is active.

Continuing immunologic research, coupled with increasing sophistication with regard to the genetic determinants of the immunologic response, should open the door for identifying a gene or genes that are responsive for

susceptibility to diabetes, and under what circumstances susceptibility becomes an active disease process. Already, we are attempting intervention at the point of immune destruction. In the future, intervention aimed at the genetically determined susceptibility may become a reality.

Research on the insulin receptor and the mechanisms of insulin action will continue to provide information on the many different levels at which metabolic defects can impair glucose homeostasis. While this work is critical to identifying the origin of noninsulin-dependent diabetes, it is also an important avenue towards a complete understanding of all forms of diabetes.

Continuing clinical research will provide us with the answers we need to refine current treatment and to ensure that those who now have diabetes can face the lowest possible risk of long-term complications. While prevention is key in approaching the complications of diabetes, there is much evidence that continuing improvement in the treatment of the complications will provide a greatly increased degree of reassurance that the onset of complications need not mean an inevitable and continuing decline in health.

One thing that is absolutely essential to keep in mind is the continuing importance of basic research as the source of the technology that has made these extraordinary advances possible.

Permit me once again to congratulate all who have had a part in bringing about this important event. Since communication among scientists is as much a part of research as laboratory and clinical procedures, I am confident that advances will result from the international exchanges that will take place here during this week.



WELCOMING REMARKS TO THE SECRETARY\*

BY

JAMES B. WYNGAARDEN, M.D.\*\*

BEFORE WE BEGIN TODAY'S CONFERENCE I WOULD LIKE TO NOTE THAT DR. MORTIMER LIPSETT, WHO DIED THIS PAST WEEKEND HERE AT THE CLINICAL CENTER, WAS A PIONEER IN RESEARCH ON THE HORMONAL ASPECTS OF BREAST CANCER. IN THIS WORK--BEFORE HE WENT ON TO SERVE AS DIRECTOR OF THE CLINICAL CENTER, DIRECTOR OF THE NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT, AND THE DIRECTOR OF THE NATIONAL INSTITUTE OF ARTHRITIS, DIABETES, AND DIGESTIVE AND KIDNEY DISEASES--HE CONTRIBUTED GREATLY TO MODERN TREATMENT METHODS FOR BREAST CANCER.

WE ARE VERY PLEASED THAT SECRETARY HECKLER HAS CHOSEN THE NATIONAL INSTITUTES OF HEALTH AS THE SITE FOR HER CONFERENCE "BREAST CANCER: A REPORT TO AMERICAN WOMEN."

SECRETARY HECKLER HAS HAD AN ABIDING INTEREST IN THE PROGRAMS OF THE NIH--ESPECIALLY THOSE OF THE NATIONAL CANCER INSTITUTE, AND A LONG-TERM COMMITMENT TO WOMEN'S HEALTH ISSUES. JUST TWO MONTHS AGO, SHE PARTICIPATED IN A MAJOR CONFERENCE HERE--A CONSENSUS DEVELOPMENT CONFERENCE ON THE TREATMENT OF BREAST

---

\*PRESENTED AT SECRETARY HECKLER'S CONFERENCE ON BREAST CANCER, NOVEMBER 13, 1985, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MD.

\*\*DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MD.



CANCER. THAT CONFERENCE WAS PRIMARILY AIMED AT PROVIDING A SYNTHESIS OF SCIENTIFIC FINDINGS FOR MEDICAL PRACTITIONERS. OUT OF THE SECRETARY'S PARTICIPATION IN THAT SESSION GREW A PLAN TO HOLD TODAY'S CONFERENCE--AIMED SPECIFICALLY AT WOMEN--TO BRING THEM UP TO DATE ON THE PROGRESS IN DETECTION AND TREATMENT OF BREAST CANCER. TO THAT END, SECRETARY HECKLER HAS CONVENED A GROUP OF NOTED HEALTH CARE PROFESSIONALS WITH EXPERIENCE IN ALL ASPECTS OF BREAST CANCER AND HAS INVITED WOMEN TO PARTICIPATE IN THEIR DISCUSSIONS.

I WANT TO WELCOME SECRETARY HECKLER AND CONFERENCE PARTICIPANTS TO THE NIH. MADAM SECRETARY.

STATEMENT  
BY  
JAMES B. WYNGAARDEN, M.D.  
DIRECTOR  
NATIONAL INSTITUTES OF HEALTH  
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE  
ENVIRONMENTAL AND ENERGY STUDY CONFERENCE  
CONGRESS OF THE UNITED STATES

NOVEMBER 14, 1985

Senator Gore, I am pleased to testify today, on behalf of the National Institutes of Health (NIH), at this hearing sponsored by the Environmental and Energy Study Conference on government oversight of biotechnology.

The primary role of the NIH in relation to biotechnology has been the support of basic biomedical research. This is discussed in a February, 1985, NIH Report on Biotechnology prepared for the Committee on Appropriations, U.S. House of Representatives, which described NIH-sponsored basic research both "directly related to or utilizing the new biotechnology" and "underlying the new biotechnology." The NIH will continue its extensive support of basic biomedical research which can be expected to lead both to many future advances in biotechnology, and to uses of biotechnology towards the better understanding, diagnosis, prevention, and treatment of human diseases.

In addition, the NIH was the first Federal agency involved in the oversight of the safety of recombinant DNA research; the NIH's role is described in detail in the NIH Guidelines for Research Involving Recombinant DNA Molecules (Guidelines). The Guidelines were first published in 1976 and have been revised many times since then. The latest complete revision of the Guidelines appeared in the Federal Register of November 23, 1984 (49 FR 46266-46291). A summary of the contents of the Guidelines is attached. As noted there, Section III-A-2 of the Guidelines covers "deliberate release into the environment of any organism containing recombinant DNA..." It is NIH's intention to continue to revise and oversee the Guidelines, and to continue the NIH Recombinant DNA Advisory Committee (RAC) and the NIH Office of Recombinant DNA Activities (ORDA), described in the Guidelines.

As you know, the Working Group on Biotechnology (originally established under the Cabinet Council on Natural Resources and the Environment; now under the Domestic Policy Council) has been meeting frequently since its creation in April 1984. The NIH has been an active participant in the meetings; I have attended most of the meetings myself, and when not able to attend, have sent another NIH representative.

The deliberations of the Working Group led to the publication for public comment in the Federal Register of December 31, 1984, of a Proposal for a Coordinated Framework for Regulation of Biotechnology (49 FR 50856-50907). That document included the statement that, "at the present time existing statutes seem adequate to deal with the emerging processes and products of modern biotechnology." I believe that assessment remains correct.

The December 31, 1984, Federal Register notice praised the work of the NIH RAC. It stated:

"The importance of the highest caliber scientific advice to the decision-making process for oversight of biotechnology is undisputed. NIH's experience with its RAC is an example of the value of using distinguished scientists to participate in the assessment of risk of new projects or proposals involving genetic manipulation. The experience of the RAC over the past ten years serves as a valuable model to the Working Group in structuring the proposed scientific review coordinating mechanism."



192

The December 31, 1984, notice proposed that four other agencies (EPA, FDA, USDA and NSF) establish scientific advisory committees similar to the NIH RAC to "provide detailed scientific review of individual applications or issues that have been submitted to them."

The December 31, 1984, notice proposed in addition to the agency-based scientific advisory committees, that a second-tier committee be established, reporting to the Assistant Secretary for Health, Department of Health and Human Services (HHS). That committee, to be called the Biotechnology Science Board (BSB), was to include two members from each agency-based scientific advisory committee.

Many of the public comments received on the December 31, 1984, notice criticized aspects of the proposed BSB. Twenty-five comments expressed concern that the two-tiered structure, with two levels of scientific advisory committees, was too cumbersome, and that the possible double review procedures could impose unreasonable delays and become a disincentive to development of new biotechnology products. Eight comments were concerned about the ability of the BSB to protect confidential business information. Seven comments were concerned that the BSB would detract from the NIH RAC, impairing its stature and function.

In light of these comments, modifications were considered by the Working Group on Biotechnology. There remained a general consensus that it was desirable to establish a committee where Federal officials could discuss scientific questions arising from applications received by the agencies, in order to promote consistency in development of agency approaches. However, there was

judged to be no need for a second-level public advisory committee. It was decided that sharing of information and coordination could be effectively carried out through an interagency coordinating committee composed of senior representatives from the involved agencies including NIH, NSF, USDA, EPA, and FDA.

Having made a decision to establish an interagency coordinating committee, the question of the proper location for the committee was considered. HHS contains within it NIH and FDA, proposed members of the coordinating committee. Locating the committee within HHS could give the impression of a bias toward an HHS point of view in areas of interagency controversy. Similarly, placing the coordinating committee within another agency could also raise the appearance of a bias towards that agency. A location apart from any single regulatory or research agency seemed to be preferable.

The Federal Coordinating Council for Science, Engineering and Technology (FCCSET) appeared to be a suitable organizational structure under which to place the coordinating committee. FCCSET is a statutorily-mandated (42 U.S.C. 6651) interagency coordinating mechanism housed within the Office of Science and Technology Policy with a mission to coordinate science activities of Federal agencies. Committees are established under FCCSET to address particular concerns. Accordingly, on October 30, Dr. G.A. Keyworth, Chairman of FCCSET, signed a charter creating a FCCSET committee to coordinate scientific issues related to research and commercial applications of biotechnology, the Biotechnology Science Coordinating Committee (BSCC).

The members of the BSCC are to be senior policy officials at the involved agencies. Initial members of the BSCC are:

Department of Agriculture

Assistant Secretary for Marketing and Inspection Services

Assistant Secretary for Science and Education

Department of Health and Human Services

Commissioner, Food and Drug Administration

Director, National Institutes of Health

Environmental Protection Agency

Assistant Administrator for Pesticides and Toxic Substances

Assistant Administrator for Research and Development

National Science Foundation

Assistant Director for Biological, Behavioral and Social Sciences

The BSCC will be chaired by the Assistant Director for Biological, Behavioral and Social Sciences of the National Science Foundation and the Director of the National Institutes of Health on a rotating basis.

The charter of the BSCC enumerates its purposes as:

To serve as a coordinating forum for addressing scientific problems, sharing information, and developing consensus;

To promote consistency in the development of Federal agencies' review procedures and assessments;

To facilitate continuing cooperation among Federal agencies on emerging scientific issues; and

To identify gaps in scientific knowledge.

The charter of the BSCC provides for the sharing of information related to scientific questions and authorizes the BSCC to receive information regarding the scientific aspects of biotechnology applications submitted to Federal research and regulatory agencies for approval. The BSCC is to conduct analyses of broad scientific issues that extend beyond those of any one agency and to develop generic scientific recommendations that can be applied to similar, recurring applications. The BSCC is authorized to convene workshops and symposia, and coordinate special studies related to scientific issues in biotechnology. The BSCC will not conduct a second-level review of applications. The BSCC discussion will not delay agency decision-making. On the other hand, it is hoped that the information discussed at BSCC meetings will provide an information base to agency officials that will in fact assist them in addressing new applications. I anticipate that deliberate release into the environment of genetically engineered organisms will be a topic dealt with extensively at BSCC meetings.



I believe the Biotechnology Science Coordinating Committee established under the Federal Coordinating Council for Science, Engineering and Technology will provide an excellent vehicle for coordination of government oversight of biotechnology.

This concludes my prepared testimony. I will be pleased to answer any questions you may have.

209

Summary of Contents of the NIH Guidelines for Research Involving  
Recombinant DNA Molecules.

Section I of the Guidelines includes: the purpose of the Guidelines; definitions of terms used; and the statement that "the Guidelines are applicable to all recombinant DNA research within the United States or its territories which is conducted at or sponsored by an Institution that receives any support for recombinant DNA research from the National Institutes of Health."

Section II of the Guidelines gives a general discussion of "physical containment" and "biological containment."

Section III of the Guidelines divides recombinant DNA experiments into four classes, i.e. "III-A. Experiments which require specific RAC review and NIH and IBC [institutional biosafety committee] approval before initiation of the experiment; III-B. Experiments which require IBC approval before initiation of the experiment; III-C. Experiments which require IBC notification at the time of initiation of the experiment; [and] III-D. Experiments which are exempt from the procedures of the Guidelines. For class III-A, it is specified that "Experiments in this category cannot be initiated without submission of relevant information on the proposed experiment to NIH, the publication of the proposal in the Federal Register for thirty days of comment, review by the RAC, and specific approval by NIH. The containment conditions for such experiments will be recommended by RAC and set by NIH at the time of approval." Four types of experiments are placed within Class III-A, i.e.: "III-A-1. Deliberate formation of recombinant

DNAs containing genes for the biosynthesis of toxic molecules lethal for vertebrates at an LD<sub>50</sub> of less than 100 nanograms per kilogram body weight...."; "III-A-2. Deliberate release into the environment of any organism containing recombinant DNA...."; "III-A-3. Deliberate transfer of a drug resistance trait to microorganisms...."; and "III-A-4. Deliberate transfer of recombinant DNA or DNA derived from recombinant DNA into human subjects...."

Section IV of the Guidelines specifies the roles and responsibilities of "each institution conducting or sponsoring recombinant DNA research covered by these Guidelines" including the Institutional Biosafety Committee, Biological Safety Officer, and Principal Investigator. Noncompliance with the Guidelines may result in "suspension, limitation or termination of financial assistance for such projects and of NIH funds for other recombinant DNA research at the Institution...." Section IV of the Guidelines also discusses the roles and responsibilities of the NIH, including the Director, NIH, the NIH Recombinant DNA Advisory Committee (RAC), and the NIH Office of Recombinant DNA Activities (ORDA). The RAC "shall consist of 25 members...appointed by the [HHS] Secretary or designee, at least fourteen of whom shall be selected from authorities knowledgeable in ... scientific fields ... and at least six of whom shall be persons knowledgeable in applicable law, standards of professional conduct and practice, public attitudes, the environment, public health, occupational health, or related fields. Representatives from Federal agencies shall serve as non-voting members." No changes in the Guidelines shall be made without publication of the proposed change for public comment in

the Federal Register at least 30 days prior to a RAC meeting, and consideration by the RAC.

Section V of the Guidelines contain footnotes and references for Sections I-IV.

Section VI of the Guidelines, entitled "Voluntary Compliance," states that "individuals, corporations, and institutions not otherwise covered by the Guidelines are encouraged to do so .... Since commercial organizations have special concerns, such as protection of proprietary data, some modifications and explanations of the procedures... are provided."

Appendix A and Appendix C of the Guidelines list certain types of experiments which are exempt from the Guidelines. Appendix B classifies disease causing microorganisms. Appendix D describes certain action taken under the Guidelines. Appendix E describes certified host-vector systems. Appendix F gives containment conditions for cloning of genes coding for the biosynthesis of molecules toxic for vertebrates. Appendix G describes physical containment and defines four Biosafety Levels (BL1, BL2, BL3 and BL4). Appendix H covers shipment of organisms containing recombinant DNA molecules. Appendix I discusses biological containment. Appendix J describes the Federal Interagency Advisory Committee on Recombinant DNA Research which met from 1976 to 1980. Appendix K gives physical containment for large-scale uses of organisms containing recombinant DNA molecules. Appendix L specifies conditions under which certain plants may be approved for release into the environment after review by the RAC Plant Working Group without review required by the full RAC.





1-07

**REMARKS\***

by

James B. Wyngaarden, M.D.\*\*

I agree with Dr. Malone's comment that occasions like this are a real pleasure. Today, with FTE reductions, increased legislative mandates, and public demands in health areas, we often do not hear about the remarkable accomplishments of our fellow workers. In fact, we are more likely to hear about problems rather than achievements and awards.

To all of you in the Office of the Director (or OD), I want you to know that the dedication, skill, imagination, enthusiasm, and plain hard work that you bring to your jobs are clearly evident. However, selecting specific individuals to honor is exceedingly difficult and can be done only with the qualification that we recognize these individuals as representative of many others who are equally deserving.

Members of OD serve the agency in many diverse areas to facilitate the conduct and support of research and research training. Although you may not work in a laboratory or clinic, you substantially influence the success of our agency in carrying out its mission. You represent the NIH to those

---

\*Presented at the Office of the Director Honor Awards Ceremony, November 14, 1985.

\*\*Director, National Institutes of Health, Bethesda, Maryland.

with whom you come in contact--counterparts in the Office of the Assistant Secretary for Health, sister agencies within PHS, other government agencies, and the private sector.

Your offices are frequently called upon to provide large amounts of information quickly and accurately. Some in OD-- for example, our security personnel--have carried out delicate and difficult tasks with grace and diplomacy. Others plan and maintain the exceptionally beautiful campus environment that we enjoy and our visitors find so delightful. You spend long nights over pages and pages of tiny figures for short turn-around budget requests, and weekends to create Congressional testimonies on 48-hour deadlines. You receive last minute or after-hours requests for transport of individuals and/or very important papers to the Department or to Capitol Hill. You devote days to smoothing and clarifying the smallest details for national and international conferences and preparing reports so that the latest research findings can be readily available to practicing physicians and the general public.

These are but a few illustrations of your quiet and consistently splendid performance. We appreciate and acknowledge all your efforts, and I offer my personal congratulations to those who will receive special honors today.

**"FEDERAL BIOMEDICAL SCIENCE POLICY"\***

by

James B. Wyngaarden, M.D.\*\*

The National Institutes of Health--for half a century or more--has been a dynamic expression of the biomedical science policy of the United States Government. Because it is the principal arm for biomedical research, I will take the liberty of discussing the policy that undergirds the NIH as if it constituted the Federal biomedical science policy. However, any discussion of our nation's science policy if it is to be complete must take place within the context of all biomedical research in this country.

Our most recent projection of total expenditures for health research and development in the United States during the current year is about \$13.5 billion. The Federal Government is expected to be the source of just over one-half of the total, or about \$6.8 billion. The National Institutes of Health alone will provide about \$4.8 billion, or 70 percent of the total Federal investment in biomedical

---

\*Breakfast address before The New York Science Policy Association at The New York Academy of Sciences, November 15, 1985.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



research. The NIH at this time is responsible for over 35 percent of the funding from all sources in the nation.

During the past decade, there has been a sizable increase in the amount of biomedical research supported by industry. Ten years ago, industry's expenditures in the United States for health research and development amounted to \$1.3 billion, or about 27 percent of the national total. In 1985, industries expect to spend about \$5 billion, or 37 percent of the national total, an amount slightly more than the share supported by NIH. That, by the way, is a change, for until two years ago, NIH expenditures had exceeded industry's total annually since World War II. In part, this increase in industrial expenditures reflects the upsurge in biotechnology, as, for example, new industries exploiting recent developments in biotechnology. It is also worth noting that along with increased expenditures by industry, new kinds of relationships have been established by industrial organizations with some of our finest academic institutions. Ingenious contractual arrangements have been developed to protect the interests of both industry and academia, with special attention to such essentials as freedom of inquiry and open scientific communication. There is much to be gained by all concerned in these new modes of cooperation.

In this connection, I should mention the increased interest in what we have come to call the "new biotechnology"--the tremendous enthusiasm surrounding the

expected payoffs from this field coupled with a deep commitment to safe applications. The fact that industry, academia, and government are cooperating so closely on the diverse and complicated issues surrounding the launch of this new era is gratifying. This level of cooperation is certainly healthy and will help in maintaining dominance in the field for the United States.

For its part, the NIH would be enthusiastic about the concepts and methodologies of the science base supporting biotechnology even absent the commercial promise. For this new science has advanced our understanding of biological mechanisms and processes in health and disease in ways that are unprecedented. Now, thanks to laboratory techniques such as recombinant DNA technology, we are beginning to make headway toward effective vaccine development in several recalcitrant fields. This is but one example. Biotechnology has had an impact on the conduct of basic biomedical research comparable perhaps to that of the computer on information processing. Biotechnology has moved us ahead by leaps and bounds in understanding cancer, genetic defects, organ transplanation biology, clinical immunology and the allergic response, and bone development and repair, just to name a few areas.

The competitive advantage this country currently holds in biotechnology is in part due to the investment by NIH over the years. In its recent report on commercial biotechnology, the Office of Technology Assessment concluded that three

factors are of overriding importance in determining a country's competitive position in world markets.<sup>1</sup> One of those three factors--funding of basic and applied science--and the supply of adequate numbers of trained personnel have been and remain a major commitment of the NIH. The third factor, availability of funds for industrial development, of course, is the responsibility of others. In its comparison of competitor countries in biotechnology, the OTA report determined that the United States, both in absolute dollar amounts and in relative terms, has the largest commitment to basic research in the biological sciences. The OTA report also concluded that the U.S. currently has a competitive edge in the supply of molecular biologists and immunologists able to meet corporate needs, in part because the U.S. Government has supplied substantial funding since World War II for basic life sciences research and research training in the U.S. universities.

NIH continues to make a major commitment to the future of biotechnology. In fiscal year 1985, it is estimated that the NIH will have provided approximately \$600 million for basic research and research training related directly to biotechnology, and almost \$1.3 billion for support of the broader science base underlying this field. By basic research directly related to or utilizing the new biotechnology, we mean genetic manipulation, cloning of DNA, use of special techniques to isolate and detect DNA, creation of hybridomas and production of monoclonal antibodies, and

computer methods used to analyze DNA and protein sequences. Basic research underlying the new biotechnology includes undifferentiated, free-ranging investigations in genetics and molecular biology, cell biology, and immunology.

The proportion of the total NIH budget devoted to biotechnology has remained constant since 1983, but about 11 percent devoted to directly related research, and about 25 percent devoted to underlying basic research and research training.

If twenty years ago the Director had talked of the NIH role with respect to biotechnology as I have done, it is likely that the discussion would have been considered as inappropriate or at best speculative. Yet at that time, much of the science base on which the new technology depends had been or was being discovered in the course of customary NIH activities.

Last summer the NIH Director's Advisory Committee, at my suggestion, set aside two days to discuss in a public forum the proper role for NIH in the arena of biotechnology policy. A recurring theme heard throughout the two-day meeting in retrospect seems to me a concise summary of the group's consensus that NIH ought to continue to do what it does best--that is, support research and research training in biomedicine--but be open-minded and flexible as to how we might further contribute to the future of biotechnology.



It is interesting--in fact reassuring--how closely the NIH experience corresponds with a general policy statement on science enunciated last year by George Keyworth, the President's Science Advisor. He talked of reviewing Federal science policies and reported, "Perhaps the most important element of policy that emerged from recent reassessments was a renewed--and considerably strengthened--commitment to Federal support for basic research. Not only is basic research an essential investment in the nation's long-term welfare, but it is largely a Federal responsibility because its benefits are so broadly distributed. Quite simply, basic research is a vital underpinning for our national wellbeing."<sup>2</sup>

In support of his assertion about the importance of basic research to the nation, he spoke of research grants to universities and the training of new talent for American technological leadership; of the generation of new knowledge to drive our economic growth, and of the formation of partnerships for development of new technologies to keep American industry competitive.

The Keyworth statement is a recapitulation of the part of the NIH history concerned with the movement from basic research to biotechnology. But permit me to return more specifically to the overall development of NIH.

In assessing what we would term NIH success in the past 10 to 20 years in advancing basic knowledge in the many

disciplines related to biomedicine, it is necessary to look beyond mere dollars invested in research and training. Since the time NIH began to develop its extramural programs shortly after World War II, we have adhered to several principles that have served us well over the years.

Foremost is the conviction that basic knowledge should be pursued largely through the support of biomedical research conducted by scientists at universities, and that the capacity of those university departments--primarily medical schools--should be strengthened wherever possible. Another guiding principle has been that the primary source of research support should be the investigator-initiated research project grant, by which mechanism we believe we can tap the most creative minds attacking the most critical problems in science.

A third important factor has been our reliance upon a peer review system of outside advisors for selection of the most meritorious proposals presented to us. This so-called dual review of grant applications consists of two sequential levels of review--first by panels of experts established according to scientific disciplines which have as their primary function the review and evaluation for scientific and technical merit, and second by the statutorially mandated national advisory councils or boards attached to the NIH bureaus, institutes, and divisions that actually make decisions on awards. The council recommendations are based not only on considerations of scientific merit, but also on

the relevance of the proposed study to NIH programs and priorities.

Over the years, this system has worked amazingly well.

The consistent support that NIH has received from successive administrations and congresses stems from a firm belief in the soundness of national investment in biomedical research. It also attests to confidence in the mechanisms that have been developed by the NIH for making such investments.

The 40-year period since the end of World War II is the era of the modern NIH--the agency as we know it today. The war years brought dramatic changes to the small Federal laboratory known then as the National Institute of Health. Almost all of its research activities until that time had been in-house but, under the stress of war, universities, medical schools, hospitals, and other laboratories were drafted into a partnership with the Federal Government to meet the pressing needs for biomedical research. The partnerships that were formed in that period have never been dissolved. The NIH, by the late 1940s, began to rely more and more heavily upon its extramural programs in carrying out its mandate. In recent years, the commitment of funds to the extramural components has represented four-fifths of the agency's total budget.

Addition of the extramural dimension to the NIH was accompanied by increases in budget--increases that for a part

of the time from 1945 to the present have been spectacular. In terms of purchasing power in constant dollars, the total budget of NIH grew from 1945 to 1968 at an astounding rate of 24 percent per year. The growth per year since 1968, taking inflation into account, has been much less--about 2 percent per year. In part, the extremely rapid growth in the earlier period resulted from expansion of the scope of the agency to the creation one by one of new institutes. Increases since 1968 have tended to be selective, with some components, programs, and mechanisms enjoying substantial increases, and other elements experiencing compensating slowdowns in growth--or actual decreases. Such adjustments have been at the heart of most budget-related policy discussions concerning the NIH for the past 15 years.

By the mid-1960s, it had become apparent that the steep climb in the NIH budget must taper off. To blunt this trend, however, dedicated proponents of our programs in biomedical research took the offensive under the banner of a war against the killers--heart disease, cancer, and stroke. By 1970, a well-planned and expertly executed initiative was responsible for what was called a declaration of war against cancer. For a time the Democratic congress and the Republican administration attempted to outbid each other in terms of appropriations and organizational innovations to hasten the conquest of cancer. Proponents of research on heart disease followed suit and were able to attract attention and increased funds, as well.



Between 1971 and 1973, the budget of the National Cancer Institute in current dollars was more than doubled. It had tripled by 1975. The National Heart, Lung, and Blood Institute also experienced a period of rapid growth, increasing by 54 percent between 1971 and 1973, and doubling by 1977. The budgets of both these institutes grew faster than the total NIH budget during the early seventies. By the late seventies, however, the growth differentials between institutes had largely evened out and a steady state had been reached.

An examination of the NIH budget for the period beginning in 1972 and continuing to the present would reveal another set of adjustments, not along institute lines but shifts in the use of the various mechanisms we fund for carrying out research. The salient feature of these adjustments was the marked shift in the allocation of funds to favor the support of research project grants. Between 1972 and 1974, the budget for research project grants increased from 44 to 66 percent of the extramural budget. There was a concomitant reduction in budget for research contracts and research training. The total number of research project grants supported during 1972 was 10,290, and by 1984 the number had grown to 17,305. Throughout this time the average award in constant dollars per project remained virtually unchanged. However, indirect costs took an increasing share of the research award, rising from 21 percent in 1972 to over 31 percent in 1984. Consequently,

the real dollars available per project for direct costs were reduced.

After 1979 when the constant dollar budget began to decline, and all possible shifts among program mechanisms had been made, it was decided that in order to maintain the number of active project grants, our only recourse was to negotiate downward not only the projected costs of competing grants but also the continuing commitments for noncompeting projects.

Another pressure has developed not directly the result of the budget crunch but an effect of the progress of science. The number of excellent applications for grants increased at a much more rapid rate than our ability to fund them. The number of competing applications for project grants reviewed in 1984 was 16,900, essentially double the number reviewed in 1971.

In the past decade we have become increasingly concerned about maintaining a relatively stable and predictable level of new and competing renewal project grants. The number of competing awards has fluctuated greatly since 1970, ranging from a total of 2,580 in fiscal year 1970 with year to year savings culminating in a high of something over 6,000 in 1985. Such fluctuations not only create financial problems for grantee institutions but adversely influence the career decisions of graduate students as well as young scientists.

We have recognized that to assure future health gains, the current national research capability must be sustained and enhanced. As applied to research project grants, a major goal was to minimize the year-to-year fluctuations in the number of competing grants. The goal of funding at least 5,000 new and competing renewal grants atop a base of moral commitments of 11,000 continuation grants was considered a major feature of the stabilization policy. While we have indeed supported at least 5,000 competing research project grants each year since 1980, budgetary limitations have precluded a comparable degree of stability for other research and training programs of the NIH.

The marked increase in the number of meritorious applications for grants characteristic of the last decade has outstripped the availability of resources and has intensified competition. In 1975, we were able to fund about 60 percent of grants eligible for award, but in 1984 the award rate was about 37 percent. From the NIH perspective, the approved but unfunded grants constitute an index of the scientific opportunities that we currently are unable to pursue. From the viewpoint of the applicant, these figures mean that an increasing number of investigators whose research careers often depend upon successful competition for grant support are failing to obtain that support.

A measure that is perhaps more meaningful to the applicant is the success rate--that is, the ratio of the number of awards to the number of applications reviewed. In

1975, the success rate was 45 percent. In 1984, it was 32 percent.

The advances in science in recent years have also brought with them the need for advances in instrumentation and facilities. Over the past decade, increasing concerns over the deteriorating institutional base for health research have been widely expressed. The most common of these concerns is the worsening state of obsolescence of research instrumentation and facilities in the nation's research universities. Some suggest that progress now being made in biomedical research may be impeded, and the momentum generated by the past investments jeopardized.

Three NIH programs are geared directly to the support of research instrumentation: the largest are the biomedical research support shared instrumentation program and the biomedical research technology program, both administered by the Division of Research Resources. The 1985 estimate for the biomedical research shared instrumentation program is about \$32 million, and for the biomedical research technology program is about \$35 million.

A study on instrumentation, jointly funded by the National Science Foundation and the NIH, has just been completed. The study, not surprisingly, will show a national need for newer equipment in many laboratories, particularly in public institutions, and emphasize the need for instruments costing between \$10,000 and \$75,000. From an



analysis of this study, we will be able to estimate the cost of restoring the instrumentation in the nation's biomedical research laboratories to an acceptable level. For years there has been a steady deterioration in the condition of academic research facilities. Federal support in this area has continued to decline. NIH is now planning a survey of the needs and status of the nation's biomedical research facilities.

In spite of the fact that virtually every major development in biomedical research has depended in part upon the use of animals, many institutions are coming under pressure from a small but determined segment of society opposed to this aspect of research. There have been break-ins at about a dozen sites and at NIH a sit-in. At other localities, there have been bomb threats and vandalism against the property of investigators and others associated with studies requiring animals.

Legislative activities on the subject at the national, state, and local levels are on the increase. There is a critical need to develop better understanding among the general public, the mass media, and elected officials on the scientific imperatives of using animals in research.

In conclusion, I will report briefly on the status of the NIH budget, and following that, respond to any questions you may wish to ask.

- <sup>1</sup> Commercial Biotechnology: An International Analysis.  
Office of Technology Assessment. Congress of the United  
States. January 1984.
- <sup>2</sup> G. A. Keyworth II. "Four years of Reagan Science Policy:  
Notable Shifts in Priorities." Science, April 6, 1984,  
p. 9.



105

## FRONTIERS IN MEDICINE AND MEDICAL RESEARCH\*

by

James B. Wyngaarden, M.D.\*\*

I am honored to have been invited to address the West Virginia University community and am especially pleased to be here tonight. As some of you may know, Ed Flink previously had asked me to speak here. I had accepted with pleasure and had set a date for the visit last February, but unfortunately our plans were not concurred in by the Congress and hearings on the NIH appropriations for 1986 were scheduled so that I had to stay in Washington. Ed was kind enough to give me a second invitation and this time I was able to come--even though the 1986 appropriation has not yet been approved, but is in the final stages of the legislative process, I am happy to say.

I was asked to talk about frontiers--frontiers in medicine and medical research. I will take the liberty of doing so mostly in the context of the programs and activities of the National Institutes of Health. For 40 years the energies and the resources of the NIH have constituted a substantial force in moving back the frontiers of medicine and medical research. As you and I know, such frontiers are movable and they move.

---

\*Presented at the School of Medicine, West Virginia University, Morgantown, November 19, 1985.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



Dr. Daniel E. Koshland, Jr., editor of SCIENCE magazine, has addressed this point incisively in an editorial appearing in the current issue of the magazine. Under the title "In Pursuit of the Renewable Frontier," Dr. Koshland wrote: "The endearing feature of intellectual frontiers is that they are in endless supply. Explorers of continents fight their way through wildernesses until they arrive at the water's edge, and then sigh that there are no new mountains to conquer. Researchers, on the other hand, are part of an ever-expanding universe, inevitably creating new territories to explore as they complete the maps begun by the discoveries of the past."

Dr. Koshland then observed that, "No area of research illustrates this phenomenon more clearly than modern biology, which many believe is in its Golden Age."<sup>1</sup>

Certainly we can all agree that in the past half century a revolution has taken place in biology--a revolution so sweeping in its scope as to transform our understanding of all living things. In little more than a generation the scientific community has witnessed the development of what has been called "a coherent if preliminary outline of the nature of life."<sup>2</sup>

The explosion in knowledge has brought new vigor into practically every branch--every discipline--of the science of biology and at the same time has created new branches. The expansion and branching surprisingly have not resulted in the fragmentation that one might expect but rather have fostered a kind of convergence.

Nobel laureate Arthur Kornberg perceived this paradox and captured its significance in a brief paragraph. He noted the extraordinary recent developments in genetic chemistry and immunology but asserted that ". . . there is an even more profound development in medical science, a change that is truly revolutionary and yet one never hears it mentioned." That development, he said, ". . . is the confluence of the many discrete and previously unrelated medical science subjects into a single unified discipline. Anatomy, physiology, biochemistry, microbiology, immunology, and genetics have now been merged and are expressed in a common language of chemistry." He maintained that "by reducing structures and systems to molecular forms, all aspects of body form and function blend into a logical framework."

Dr. Kornberg added, "There is no doubt that this revolutionary confluence of the medical sciences was made possible by the massive Federal grants programs of the National Institutes of Health and the National Science Foundation in the postwar period."<sup>3</sup>

The 40-year period since the end of World War II is the era of the modern NIH--the agency as we know it today. The war years brought dramatic changes to the small Federal laboratory known as the National Institute of Health. Almost all of its research activities until that time had been inhouse, but under the stress of war, universities, medical schools, hospitals, and other laboratories were drafted into a partnership with the Federal Government to meet the pressing needs of the military for medical research. The partnerships that were formed in that period have

never been dissolved. The NIH by the late 1940s began to rely more and more heavily upon its extramural programs in carrying out its mandate. In recent years, the commitment of funds to the extramural components has represented four-fifths of the agency's total budget.

Addition of the extramural dimension to the NIH was accompanied by increases in budget--increases that for a part of the time from 1945 to the present have been spectacular.

In terms of purchasing power in constant dollars, the total budget of NIH grew from 1945 to 1968 at an astounding average rate of 24 percent per year. The growth per year since 1968, taking inflation into account, has been much less--about 2 percent per year. In part, the extremely rapid growth in the earlier period resulted from expansion of the scope of the agency through the creation, one by one, of new Institutes. Increases since 1968 have tended to be selective, with some components' programs and mechanisms enjoying substantial increases and other elements experiencing compensating slowdowns in growth or actual decreases. Such adjustments have been at the heart of most budget-related policy discussions concerning the NIH for the past 15 years.

By the mid-1960s it had become apparent that the steep climb in the NIH budget must taper off. To blunt this trend, however, dedicated proponents of our programs of biomedical research took the offensive under the banner of a war against the killers--heart disease, cancer, and stroke. By 1970 a well-planned and

expertly executed initiative was responsible for what was called a declaration of war against cancer. For a time, the Democratic Congress and the Republican Administration attempted to outbid each other in terms of appropriation and organizational innovations to hasten the conquest of cancer. Proponents of research on heart disease followed suit and were able to attract increased attention and funds.

Between 1971 and 1973, the budget of the National Cancer Institute in current dollars was more than doubled. It had tripled by 1975. The National Heart, Lung, and Blood Institute also experienced a period of rapid growth, increasing by 54 percent between 1971 and 1973 and doubling by 1977. The budgets of both these Institutes grew faster than the total NIH budget during the early 70s. By the late 70s, however, the growth differentials between Institutes had largely evened out and a steady state had been reached.

An examination of the NIH budget for the period beginning in 1972 and continuing to the present would reveal another set of adjustments, not along Institute lines but shifts in the use of various mechanisms we fund for carrying out research. The salient feature of these adjustments was the marked shift in the allocation of funds to favor the support of research project grants. In the period from 1972 to 1984, the budget for research project grants increased from 44 to 66 percent of the extramural budget, and that for research grants from 66 to 85 percent. There was a concomitant reduction in budget for research contracts and research training. The total number of research project grants



supported during 1972 was 10,290, and by 1984 the number had grown to 17,305. Throughout this time, the average award per project remained virtually unchanged in constant dollars but increased from an average of \$59,000 to \$135,000 in current dollars. However, indirect costs took an increasing share of the research award, rising from 21 percent in 1972 to over 31 percent in 1984. Consequently, the real dollars available per project for direct costs were reduced.

In the past decade, we have become increasingly concerned about maintaining a relatively stable and predictable level of new and competing renewal project grants. The number of competing awards has fluctuated greatly since 1970, ranging from a total of 2,580 in FY 1970 with year to year swings culminating in a high of something over 6,000 in 1985. Such fluctuations not only create financial problems for grantee institutions but adversely influence the career decisions of graduate students as well as young scientists.

We have recognized that to assure future health gains the current national research capability must be sustained and enhanced. As applied to research project grants, a major goal was to minimize the year-to-year fluctuations in the number of competing grants. The goal of funding at least 5,000 new and competing renewal grants, atop a base of moral commitments of 11,000 continuation grants, was considered a major feature of the stabilization policy. While we have indeed supported at least 5,000 competing research project grants each year since 1980, budgetary

limitations have precluded a comparable degree of stability for other research and training programs of the NIH.

The marked increase in the number of meritorious applications for grants characteristic of the last decade has outstripped the availability of resources and has intensified competition. In 1975, we were able to fund about 60 percent of grants eligible for award, but in 1984 the award rate was about 37 percent. From the NIH perspective, the approved but unfunded grants constitute an index of the scientific opportunities that we currently are unable to pursue. From the viewpoint of the applicant, these figures mean that an increasing number of investigators whose research careers often depend upon successful competition for grant support are failing to obtain that support.

A measure that is perhaps more meaningful to the applicant is the success rate--that is, the ratio of the number of awards to the number of applications reviewed. In 1975, the success rate was 45 percent. In 1984, it was 32 percent.

In assessing NIH's success in the past 40 years in advancing basic knowledge in the many disciplines related to biomedicine, it is necessary to look beyond dollars invested in research and training. Since the time NIH began to develop its extramural programs shortly after World War II, we have adhered to several principles that have served us well over the years.

Foremost is the conviction that basic knowledge should be pursued largely through the support of biomedical research conducted by scientists at universities, and that the capacity of

those university departments--primarily medical schools--should be strengthened wherever possible. Another guiding principle has been that the primary source of research support should be the investigator-initiated research project grant, by which mechanism we believe we can tap the most creative minds attacking the most critical problems in science.

A third important factor has been our reliance upon a peer review system of outside advisors for selection of the most meritorious proposals presented to us. This so-called dual review of grant applicants consists of two sequential levels of review--first by panels of experts established according to scientific disciplines which have as their primary function the review and evaluation for scientific and technical merit, and second by the legislatively mandated national advisory councils, or boards, of the NIH bureaus, institutes, and divisions. If a grant is to be made it must have been recommended by an advisory council or board. The recommendations are based not only on consideration of scientific merit but also upon the relevance of the proposed study to NIH programs and priorities. Over the years, this system has worked amazingly well.

The consistent support that NIH has received from successive Administrations and Congresses stems from a firm belief in the soundness of national investment in biomedical research. It also attests to confidence in the mechanisms that have been developed by the NIH for making such investments.

The advances in science in recent years have also brought with them the need for advances in instrumentation and in facilities. Over the past decade, increasing concerns over the deteriorating institutional base for health research have been widely expressed. The most common of these concerns is the worsening state of obsolescence of research instrumentation and facilities in the nation's research universities. Some suggest that progress now being made in biomedical research may be impeded and the momentum generated by the past investments jeopardized.

Three NIH programs are geared directly to the support of research instrumentation: the principal mechanisms are the Biomedical Research Support Shared Instrumentation Program and the Biomedical Research Technology Program, both administered by the NIH Division of Research Resources. The 1985 estimate for the Biomedical Research Support Shared Instrumentation Program is about \$32 million, and for the Biomedical Research Technology Program about \$35 million.

A study on instrumentation jointly funded by the National Science Foundation and the NIH has just been completed. The study not surprisingly will show a national need for newer equipment in many laboratories, particularly in public institutions, and emphasize the need for instruments costing between \$10,000 and \$75,000. From an analysis of this study we will be able to estimate the cost of restoring the instrumentation in the nation's biomedical research laboratories to an acceptable level.



For years there has been a steady deterioration in the condition of academic research facilities. Federal support in this area has continued to decline. NIH is now planning a survey of the needs and status of the nation's biomedical research facilities.

In spite of the fact that virtually every major development in biomedical research has depended in part upon the use of animals, many institutions are coming under pressure from a small but determined segment of society opposed to this aspect of research. There have been break-ins at about a dozen sites, and at NIH a sit-in. At other localities there have been bomb threats and vandalism against the property of investigators and others associated with studies requiring animals.

The number of legislative proposals on the subject at the national, state, and local levels is on the increase. There is a critical need to develop better understanding among the general public, the mass media, and elected officials on the scientific imperatives of using animals in research.

Before responding to any questions you may wish to ask, I will report briefly on the status of the NIH budget.

As I mentioned earlier, Congressional consideration of the NIH budget for 1986 is in its final stages. Both Houses of the Congress have acted on the appropriations for NIH, but since the House and Senate versions differ, a Conference Committee must be assigned the task of resolving the differences. At the moment we are awaiting action by the Conference Committee. As you know, the

Congress has been preoccupied with the debt ceiling and deficit legislation.

It is encouraging to note, however, that both the House and Senate approve increases for the NIH as a whole. The Senate total was \$5,466 billion, an increase of 6.4 percent over 1985, and the House version calls for a slightly larger increase, 6.7 percent.

The House bill would permit 5,843 new and competing renewal research grants at an average of \$163,000 per grant. The Senate action would permit 6,006 new and competing renewal grants at \$160,000 average cost.

The House approved the payment by NIH of full indirect costs on grants, and the Senate accepted the Administration's proposal to freeze indirect cost rates at the FY 1985 level.

Meanwhile, we are well into fiscal year 1986 (which began October 1), operating at the 1985 level as prescribed by the Second Continuing Resolution--a stopgap appropriation that is scheduled to run into early December.

That is the general picture. At this time I will be glad to respond, insofar as I am able to do so, to questions about the budget or other facets of the operation of NIH.

REFERENCES

1. Daniel E. Koshland, Jr. Science, November 15, 1985, p. 743.
2. Horace Freeland Judson. "The Eighth Day of Creation."  
Simon and Schuster, New York, p. 10.
3. Arthur Kornberg. Unpublished paper, titled "Biology and  
Technology," April 13, 1982, p. 6.

## COMMENTS\*

by

James B. Wyngaarden, M.D.\*\*

Dr. Korn, Dr. Orloff, distinguished colleagues, ladies and gentlemen--good evening. Welcome to this, the annual lecture in honor of Dr. G. Burroughs Mider, another in a continuing series of NIH lectures.

Tonight we are privileged to hear Dr. Edward Korn discuss the biochemical regulation of actomyosin-dependent cell motility. Dr. Korn is Chief of the Laboratory of Cell Biology in the National Heart, Lung, and Blood Institute. He began his career at NIH in 1953 as a Damon Runyon Fellow in the Laboratory of Cellular Physiology and Metabolism in what was then the National Heart Institute. He has been with us since then, advancing to Research Chemist in the same laboratory and, in 1969, to Head of the Section on Cellular Biochemistry and Ultrastructure in the Laboratory of Biochemistry. He attained his present status as a laboratory chief in 1974, and assumed additional responsibilities as Deputy Scientific Director of NHLBI in 1982.

Dr. Korn obtained his Ph.D. from the University of Pennsylvania. He has served as a visiting scientist at Cambridge University in England and as a Professor in the Johns Hopkins University Graduate Program. His research has centered on the regulation of contractile proteins in non-muscle cells.

Basically, many types of cell motility depend on the interaction between actin and myosin, the two principal contractile proteins of muscle. The functional interaction of actin and myosin is regulated by the hydrolysis of adenosine triphosphate and by the phosphorylation and dephosphorylation of myosin.

I am certain that Dr. Korn will provide an interesting and informative lecture on these processes as he unravels the secrets of the regulation of cell motility. Without further delay, let me introduce Dr. Korn.

---

\*For Dr. Edward Korn on the occasion of the Mider Lecture, Masur Auditorium, on December 4, 1985.

\*\* Director, National Institutes of Health, Bethesda, Maryland.







DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health  
Bethesda, Maryland 20205  
Building : Shannon  
Room : 228  
(301) 496- 1454

December 10, 1985

NOTE TO: Dr. Wyngaarden

Attached are your talking points for the December 16 DAC which have been revised based on your's and Dr. Raub's comments.

A handwritten signature in cursive script, reading "Dennis Rodrigues", is positioned above the printed name.

Dennis Rodrigues

Attachment

Dr. Wyngaarden's  
Introductory Remarks for the  
December 16 Director's Advisory Committee Meeting

- Approximately two years ago on November 7, 1983, I talked at the annual meeting of the Association of American Medical Colleges about what I believe is necessary to preserve the scientific enterprise. I emphasized four goals for maintaining excellence.
- I called for the ability to award 45-50 percent of approved applications for research support. While we have not retained that level, our ability to support the number of competing awards has increased by 20 percent.
- I described the rationale for increased support of research training and called the stipends available for support of National Research Service Award trainees "paltry." Postdoctoral stipends have been raised to more nearly adequate levels to encourage preparation for research training careers. Simultaneously, most NIH Institutes were able to initiate the Physician Scientist Award with increased funding for career development.
- The other two essential elements for support of the research enterprise which still deserve attention have been addressed more in discussion than in action. I refer to the need for new research facilities to replace those that have deteriorated and the need to replace or purchase the increasingly sophisticated instruments required for today's research.

- At that time I said, "it is estimated that \$20 million a year for five years is needed for the acquisition of large-scale, shared instrumentation resources with additional funds for the purchase through research grants of smaller instruments." I am pleased to report that increased funding for the larger shared instrumentation resources has materialized; however, I would now call for a sustained program rather than a five-year solution.
- What has not been improved and what, in fact, may be slipping even further behind, is the situation involving smaller instruments in the \$10,000 to \$60,000 range.
- Before we proceed, however, I would like to ask Dr. Kirschstein to give us a brief follow-up on what has taken place regarding our last DAC meeting on the new biotechnology.

#### Instrumentation as an NIH Concern

- Early in the 1970's, leaders in the academic community argued that institutions of higher education could not keep pace with the need for upgrading and acquiring new instruments and that research advances were being impeded by the use of faulty or obsolete instruments.



- Over the next 15 years the problem was examined by a variety of groups including NIH, the National Science Foundation, the National Academy of Sciences, and the American Association of Universities.
- A number of studies were published, most of which were concerned with universities in general rather than specifically focused on the health science institutions. I will just mention a few of the reports published within the past 10 years.
- Smith and Karlesky received a grant from the National Science Foundation in 1975 to study the future research role of the universities. In their discussion they pointed out that one of the factors contributing to the apprehension about the health of the research enterprise was the deterioration of instrumentation.
- The National Science Foundation Advisory Council (then the National Science Board) reviewed a report on equipment needs in 1978 which was based on data from an NSF in-house sampling from the different directorates representing science and engineering disciplines. Their principal findings regarding research instruments indicated:
  - There was inadequate funding for equipment maintenance and acquisition;
  - Support levels were not keeping pace with inflation and the rising costs of increasingly sophisticated instruments; and

- There was a drop in the level of support by other agencies, and State and private sources.
- Gomberg and Atelsek published a report for the American Council on Education in 1980 whose principle findings showed that:
  - During 1978 approximately \$280 million was expended at Ph.D. granting institutions for purchase of scientific research equipment,
  - Half of that amount was being used in the life sciences,
  - Fifty-nine percent of the funds were expended by public institutions and 75 percent by private institutions, and
  - The Federal Government financed 65 percent of the equipment purchases.
- In April 1984, the Government Accounting Office (GAO) reviewed all prior studies identified as pertinent to the topic and analyzed them to determine the current magnitude of research equipment needs. They maintained that:
  - None of the past studies could provide a current estimate of the magnitude of research instrument needs; and

- Most of the studies suffered serious deficiencies in their scope, timeliness, methodology, or completeness.
- Two studies, however, were commended.
  - One was a 1971 report from the National Academy of Sciences for its use of a representative sample of Universities and the peer review procedures it used to validate the stated needs.
  - The second was a planned survey on academic research equipment in the physical and computer sciences and engineering. This survey was later expanded to include the biological and medical sciences. GAO judged that this survey presented the best opportunity for assessing current research equipment needs. To aid in today's discussion we have distributed the final report of that survey to you as part of your briefing material.
- You have also received a copy of a report entitled, Financing and Managing University Research Equipment, developed by the Association of American Universities.
- Also in 1985, a publication from the NAS Committee to Survey Opportunities in the Chemical Sciences, chaired by George Pimentel, reinforced the need for Federal support of instrumentation, maintenance and operating costs.

- In addition to these studies, in August, 1981, the Office of Science and Technology Policy prevailed upon the National Science Foundation to form an interagency working group on university research instrumentation.
- The membership was designed to insure the highest agency level of participation in restoring the research instrumentation capabilities of the nation's universities. This working group has met approximately twice a year to exchange information on the extent of the member agencies' support of research instrumentation. It is the impression of those of us who attend those meetings that the group activities have contributed to the improvement of agency budgets for research instrumentation. At the least, we can say that all of the agencies involved, for whatever reason, have had increased support available for research instrumentation since 1983.
- At the most recent meeting of the working group in September, all representatives felt that the current emphasis on research instrumentation is expected to continue.
- The NSF projects that approximately \$270 million of its budget will be available in research equipment and instrumentation in 1987. That is approximately 20 percent of its research project resources.
- The Department of Defense will be completing the fifth year of a five year program offering \$30 million a year for university



instrumentation. All in all, DOD estimates that between 10 and 15 percent of the budget for project support at universities is used for instrumentation.

- The Department of Energy also estimates that at least 10 percent or \$40-45 million of their \$450 million support in individual research projects will be spent on instrumentation. In addition, they provide a special university research instrumentation program for support of instruments costing \$100,000 or more which they anticipate will operate in the range of \$5 million per year starting in 1987.
- It is interesting to note that NIH appears to be putting the smallest percentage, albeit a substantial sum, of its research project resources into instrumentation when compared to the other agencies. In FY 1985 it is estimated that \$144 million, approximately 4.2 percent of a \$3.4 billion research award base, was budgeted for research instrumentation.
- A comparison across agencies must take into account the differing nature of research activities undertaken by NSF, DOD, and DOE. Research in high-energy physics, astronomy, electronics, and oceanography often involve extremely large and expensive types of equipment.

- The Congress clearly is maintaining a sustained interest in this subject, and, in the past, has expressed frustration at the lack of objective data and the resulting confusion between what is necessary and what is desirable.
- The instrumentation survey, performed by Westat, Inc., was the NSF response to the insistence of the Congress for the receipt of valid information about research instrumentation needs and its effect on the nation's competitiveness in biotechnology. The portion concerned with the needs in biological and medical science was supported by the NIH and contains the most complete and objective data yet collected. You will note, however, that no specific dollar recommendations are made.
- (SLIDE 1) This table provides some information on the current trend in the overall level of NIH support for instruments as a percent of research grant support. You will note that since 1982 the percentage of dollars supporting instruments has increased.
- The 4.2 percent figure for the NIH, when taken in context, represents a positive indication of our investment in research instrumentation.
- Despite this increase, the instrumentation survey indicates that we should pay greater attention to instrumentation in the \$10,000 to \$60,000 range. This is primarily the category involving replacement

of barely functioning, worn out, or inadequate equipment which should be replenished through the R01 mechanism.

- The data concerning the most needed instruments rely primarily on the informed opinion of department chairmen. I do not, however, think the main issues are subjects for debate. As a matter of fact, it is possible to carry informed opinion one step further and make some projections of need from the data presented.
- In effect, one member of the NIH staff has estimated a cost of \$190 million over and above what was available from all sources to replace obsolete instrumentation in the life and medical sciences in 1984. The Federal share of this sum would amount to approximately \$100 million of which NIH should contribute approximately \$80 million. This figure is over and above what we are currently providing on R01s to equip new investigators and the ongoing shared instrumentation program.
- The issue of the drain on institutions in maintaining larger items of equipment necessary for research must also be addressed. It was brought to the attention of the House Science and Technology Committee at the May 1985 Hearings of the Task Force in Science Policy. "It would be prudent for granting agencies to consider policies for funding capital equipment that would provide money for maintenance, upgrading, operation, and the training and hiring of technical personnel." Almost all of the cited reports call for some

action on this subject. For example, the Pimentel report recommends that the maintenance and operating costs should be provided for the first five years following purchase. To what degree, one can ask, should the NIH support maintenance contracts and specialized technical assistance?

- The instrumentation survey has suggested some other questions including:
  - Does the estimate of replacement costs for currently obsolete equipment as generated by the survey provide sufficient background for reasonable action?
  - Is the NIH paying adequate attention to the funding of maintenance and repair of research equipment?
  - How should NIH approach the issue that the greatest need for instrumentation is stated to be in the \$10,000 to \$60,000 range?
- Based on the assumption that what is past is prologue, I have asked Dr. Betty Pickett, Director of the Division of Research Resources, to review the NIH trends in research instrumentation support and to bring us up to date on the current status of research instrumentation programs.



INSTRUMENT COSTS AS A PERCENT OF  
NIH RESEARCH GRANT SUPPORT  
(dollars in millions)

	<u>Total R&amp;D Grants*</u>	<u>Equipment Costs**</u>	<u>Percent</u>
1975	\$1,078	\$ 50	4.6
1976	1,463	57	3.9
1977	1,362	59	4.3
1978	1,555	68	4.4
1979	1,858	85	4.6
1980	2,062	79	3.8
1981	2,233	73	3.3
1982	2,311	75	3.2
1983	2,606	90	3.4
1984	2,985	109	3.7
1985 est.	3,444	143	4.2

---

\*Excludes RCP, BRS, and Scientific  
Evaluation Grants.

\*\*Includes BRSG-shared instrument  
program, 1982-85.

"CLINICAL RESEARCH AND COST-EFFECTIVE HEALTH CARE"

by

James B. Wyngaarden, M.D.\*\*

I am very happy to be here today to participate in the celebration of the 25th anniversary of the Emory General Clinical Research Center. During my years in the Department of Medicine at Duke, I was intimately involved with the Duke GCRC and thus understand the excitement and enthusiasm that can be generated in such a clinical research setting. But it was not until I came to NIH as Director and learned more about history of the GCRC program and its evolution that I began to appreciate more fully the GCRC as a national resource, contributing in major ways to fulfilling our commitment to support clinical research and train clinical investigators.

The research accomplishments emanating from this GCRC, from the entire network of GCRC's and, indeed, from the biomedical research community as a whole over the past 25 years have been remarkable. We can feel proud of the advances in the prevention, diagnosis and treatment of disease that have derived from this national effort.

Dr. Krause will well remember that in years past, NIH Directors and Institute Directors could stand before the appropriations committees of the Congress and make the case for additional research funding by reviewing the research advances that had already had an impact on improving the health of Americans, and forecasting what we might expect in the future in terms of reductions in mortality and morbidity. The implicit promise that our efforts would eventually help people was often enough to assure budget increases for research.

More and more often in recent years, I am pressed with questions about the payoffs of biomedical research in economic terms. I am increasingly asked to justify our mission in terms of its impact upon the economy. There are several aspects of this topic that I want to talk about today.

The concern about the cost of health care and the possible impact of biomedical research upon the cost of health care makes sense when you consider the following:

o The nation is now spending 10.5 percent of the gross national product on health, twice the 1960 figure.

---

\* Commemorative Lecture at 25th Anniversary of Clinical Research Center at Emory University in Atlanta, December 18, 1985.

\*\* Director, National Institutes of Health, Bethesda, MD.

o National outlays for health, which were \$355 billion in 1983, could jump by as much as \$100 billion a year in 1983 dollars by the end of the century and reach 14 percent of the GNP solely from the added costs of new technology.\*

But, I would like to give this matter of cost-effective health care a certain perspective.

It would be difficult to improve on the cost-effectiveness of the health care system described by Herodotus some 2,450 years ago. "The Babylonians have no physicians," he said, "but when a man is ill, they lay him in a public square and the passersby come up to him. And if they have ever had this disease themselves or have known anyone who has suffered from it, they give him advice, recommending him to do whatever they found good in their own case or in a case known to them. No one is allowed to pass the sick man in silence without asking him what his ailment is."<sup>1</sup>

Undeniably, this form of treatment was inexpensive. Furthermore, it represented probably the most enlightened therapy of the day. The sad fact is that as recently as the early 1900s, medical practices in this country were little better than the Babylonian method and in some instances they were worse. For it was at the beginning of this century when thoughtful clinicians began to recognize that almost all of the complicated treatments long in common use did not work, and that many of them actually did more harm than good.

In the wake of the virtual revolution in the practice of medicine in the past fifty years, however, we have seen the development of a new array of complicated diagnostic procedures and treatments.

We are experiencing a kind of repeat of the medical history of the nineteenth century, but with a major difference. The many complicated, expensive, and often painful treatments of that day were of little if any benefit. Some procedures today may be complicated and expensive, but they are also powerfully effective.

The satisfaction we are justified in feeling about the many innovations of medicine is intruded upon, however, by our uneasiness over the economic as well as other stresses they may generate.

Moreover, this kind of progress in the application of science to health has stimulated expectations. People today are being taught to expect good health care. In the past--throughout history--illness, plagues, and personal injury were accepted as

normal events. This is no longer the case. The ability of medicine to control or eradicate disease--mostly a legacy of modern research--has brought into being new hopes and demands. Inevitably, such a collective demand has major economic implications.

The modern era of medicine is marked by successful intervention and prevention efforts both of which are increasingly science-based.

The focus of prevention has broadened considerably in recent years. Now that infectious diseases such as smallpox, diphtheria, and polio are no longer a threat to public health, preventive medicine faces a difficult challenge, namely, to eliminate those diseases that are chronic in nature, such as cardiovascular disease, cancer, diabetes, and kidney disease--diseases for which there appear to be no simple causes or solutions. Accordingly, prevention research has become both more comprehensive and complex. With progressive fine-tuning, epidemiologic research has opened new opportunities as risk factors are identified that allow new and effective strategies for prevention, with concomitant reductions in health-care costs. The role of smoking in cancer, chronic bronchitis, and heart disease is a well-known example. Control of hypertension and attention to body weight, diet, and exercise play important roles in the recent reductions of mortality from cardiovascular and cerebrovascular disease. New insights into possible dietary factors in cancer give promise of possible reductions of certain kinds of neoplasms.

From its earliest beginnings, a primary goal of the NIH has been to support and conduct research that ultimately could lead to the prevention of disease. When such efforts are fully successful, the saving in human and economic terms are great indeed. For example, the prevention of type B hepatitis through a low-cost effective vaccine could save the United States about \$145 million a year, and this figure does not take into account the hepatitis B-related liver cancer that presumably would also be prevented through vaccination.

And we can expect more benefits from vaccine development. Under the leadership of Dr. Krause, the National Institute of Allergy and Infectious Diseases initiated a program for the accelerated development of new vaccines. Studies are in progress on more than 50 vaccine antigens for over 30 different bacterial, viral, and parasitic diseases.

Preventive medicine has scored some remarkable triumphs and promises more. But, for many diseases, gains in scientific knowledge so far have brought us only to the point of amelioration of symptoms or a slowing or halting of the progression of the disease process.



Many highly technical procedures for diagnosis and treatment now coming into frequent use are truly miracles of modern medicine, but often they are very expensive and constitute a powerful force driving upward the cost of medical care. In the context of these developments, we encounter a paradox; namely, that a substantial number of medicine's discoveries in recent years have increased rather than decreased the cost of medical care. Experts in health care and research are warning that costly medical procedures--coronary bypass surgery, sophisticated new imaging systems, heart and liver transplants--could result in vast additional health outlays in the next decade.

In this regard, we are left with two challenges: First, to continue research that will bring us beyond the highly expensive halfway point in treatment of disease--as has been the mission of the NIH and institutions such as this for at least a century. And second, to develop data more useful in convincing those who make decisions about spending for biomedical research, that our work also contributes to cost savings in health care.

In an attempt to gather some data to counter the general view that research advances tend to drive up the cost of health care, I recently asked the various NIH components to provide some examples of advances in biomedical research that have reduced health care costs. Although we must consider these as estimates, based by necessity on assumptions, you may find a few of them interesting:

o Research supported by NHLBI conducted on sheep in San Francisco implicated prostaglandins in maintaining patency of the ductus arteriosus. This led to treatment of newborns with the patent ductus syndrome with the prostaglandin synthetase inhibitor, indomethacin for medical closure of the ductus. This treatment is successful in about 85% of cases. The National Heart, Lung, and Blood Institute (NHLBI) has estimated that use of indomethacin in patent ductus arteriosus (DPA) as a substitute for surgical treatment saves approximately \$180 million annually. We have estimated that approximately 20,000 premature infants have significant PDA necessitating treatment and that each surgical procedure would cost \$3,000, with an additional \$6,000 per patient for 6 days in an ICU. On the other hand, we estimate that a full course of medication costs only \$40 per patient. The research leading up to this net savings, including basic research and clinical trials, cost only about \$10 million.

o Based on results of their Coronary Artery Surgery Study, the NHLBI estimates that approximately 25,000 coronary bypasses could have been deferred in 1983 in favor of management through medical care and drugs. If the indications from the study were

widely applied, there would be the potential for reducing these health care costs for these 25,000 patients from nearly \$506 million to a little more than \$8 million, for an annual net savings of nearly \$500 million. This study cost NIH \$26.5 million over 10 years.

o A more recently reported study is the clinical trial supported by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) indicating that a widely used neurosurgical procedure to prevent stroke or stroke death, is no more effective than aspirin and standard hypertension control. If the conclusions of this study were followed widely, it is believed that thousands of extracranial/intracranial (EC/IC) bypasses now performed annually in the U.S. at an estimated cost of \$15,000 per operation could be avoided with savings of at least \$30 million.

Antenatal steroid therapy in high risk pregnancies has proved to be of benefit in the prevention of neonatal respiratory distress syndrome. The NHLBI estimates net annual savings of about \$295 million from this new therapy based on 50,000 cases of neonatal RDS per year. The clinical trial to study the efficacy of the steroid treatment cost approximately \$5.5 million.

o Aside from major clinical trials, savings from the gradual accumulation of knowledge applied by degrees, can lead to tremendous savings difficult to quantitate. Advances in diagnostic imaging techniques have had an enormous impact both in reduction of health care costs and increased safety and comfort. Today, brain tumors can effectively be diagnosed and followed for response to treatment with a simple 45-minute outpatient computer tomography scan. Before this development, diagnostic procedures were likely to include costs for EEGs, nuclear medicine scans, arteriograms, or pneumoencephalograms. Similarly, pretreatment staging of a child with Wilm's tumor might have included intravenous pyelogram, inferior vena cavogram, or retrograde pyelogram. Not only did these procedures give a relatively poor characterization of the tumor, but they were both expensive and uncomfortable, making it difficult to repeat studies and follow disease response.

o Therapy of soft tissue sarcomas, with wide local excision and radiation, rather than by amputation and subsequent prostheses, reduces the cost of treatment per person from \$50-80,000 to \$8,500. NCI intramural clinician-scientists along with others have shown this new mode of treatment to be efficacious in an increasing number of selected patients. However, while this is a saving for individual patients, it would not have a great impact in the aggregate, as this type of cancer is relatively rare.

o The National Eye Institute developed fairly solid figures relating to laser treatment for several blinding conditions. For three such disorders--angle-closure glaucoma, aging-related maculopathy, and diabetic retinopathy--taken together, laser treatment has lowered annual costs from about \$260 million to about \$106 million. Because no effective therapy was available for two of these conditions prior to development of laser treatment, the annual costs were based on estimates of the annual cost to society for support of blind individuals. Interestingly, the research leading up to the laser therapies--excluding basic research--cost only about \$13 million. This was primarily the cost of running the clinical trials to prove efficacy.

o Another noteworthy example is percutaneous transluminal coronary angioplasty in which the late Dr. Gruntzig pioneered. It was estimated by the NHLBI that 17,000 coronary artery bypass graft procedures for single vessel disease could be treated by angioplasty. . . Estimating a cost of \$20,000 per patient for the surgery as compared with \$6,800 for each angioplasty, the annual savings would be more than \$156 million, even when you consider that about 20% of the patients initially having angioplasty would subsequently require a bypass graft.

o Advances relating to child health have enormous potential for saving in health care costs. The National Institute of Child Health and Human Development (NICHD) estimates that owing to our current ability to assess fetal maturity and thus prevent prematurity associated with cesarean delivery, we are annually saving approximately \$325 million, with the problem almost entirely eliminated. Development of a screening test for hypothyroidism--at a cost of about \$1 million for research--has reduced annual costs. From about \$14 million for treatment to only \$3.5 million for screening.

o The development of specific criteria on which to base the decision on whether or not to intervene surgically to relieve recurrent throat infections has led to a large decrease in unnecessary tonsillectomies. It is estimated that development of the criteria based on NICHD-supported studies saved about \$818 million in 1985 based on a cost of \$1300 per case.

Looking at the economics of research in a different way, Selma Mushkin in her book published in 1979 addressed the question--"Is the public getting an appropriate return for the multibillion dollar yearly expenditure on health research?" The answer was an emphatic "yes" when the yardstick included actuarial estimates of the dollar value of the productivity of the lives saved and the years of sickness averted. For the 75-year period beginning in 1900, the ratio of total cumulative benefits to total research and development costs was about 13 to 1. In more recent years since 1930, the ratio was 5 to 1. The



recent somewhat lower but substantial return reflects the costs of the large amount of basic research conducted during the past 40 years. The payoff from such research is certain to strongly and favorably affect future ratios of benefits to costs. Current expenditures for basic research are long-range investments.

But in spite of such examples, the list of human diseases for which there are as yet no definitive measures for prevention or cure is still formidable. Fresh insights into the nature of these diseases are needed. And these insights can come only from continued basic research. I do not believe that there is an abundance of scientific knowledge locked in the laboratory merely awaiting a new emphasis on human application as some have claimed. Most of the critical bits of knowledge have yet to be discovered.

About a year and a half ago, I participated with Bill Schwartz of Tufts in a program at the International Congress of Nephrology where there was much discussion of the economics of technology and the cost of medical care. During a press conference that Bill and I held after our presentations, I speculated facetiously that someone will someday suggest to the Office of Management and Budget that the best way to control cost is to shut down the NIH. This was reported in The Los Angeles Times. About two weeks later, I received a letter from another Schwartz, this time Harry Schwartz, long with The New York Times and now a writer and lecturer on medical issues. He pointed out that my prediction had been fulfilled before I made it, that he had been the someone who would someday suggest shutting down research to save on the cost of medical care. He sent me a copy of an article of his that appeared in The Wall Street Journal, April 3. "Do we really want medical progress," the article began, "or should we start thinking seriously of closing the National Institutes of Health and other public and private facilities now doing research to cure diseases and prolong lives?"

In spite of the high cost of contemporary medicine, I remain optimistic not only about the future of NIH, but also the future of medical care, and believe that if we persist, one by one these expensive technologies that are now life saving will be rendered as obsolete as the iron lung and replaced by yet more effective, simpler, inexpensive measures. But we must continue to search.

In closing, permit me to use the familiar quotation from Lewis Thomas, in which he added "halfway technology" to our lexicon and stated a truth about which we need to be reminded periodically. Here are his words: "I say that we must continue doing biomedical research on about the same scale and scope as in the past 20 years with expansion and growth of the enterprise being dependent on where new leads seem to be taking us. It is



an expensive undertaking . . . but it is still nothing like as expensive as trying to live with the halfway technologies we are obliged to depend on in medicine today; if we are to try to stay with these for the rest of the century, the cost will go through the ionosphere."

\* According to the American Enterprise Institute

## REFERENCES

- <sup>1</sup>HERODOTUS, "THE HISTORY," FIRST BOOK (197), GREAT BOOKS OF THE WESTERN WORLD,  
ENCYCLOPEDIA BRITANNICA, VOL. 6, 1952, P. 44.
- <sup>2</sup>LEWIS THOMAS, THE MEDUSA AND THE SNAIL, THE VIKING PRESS, NEW YORK, 1979, P. 162.
- <sup>3</sup>HAROLD HIMSWORTH, SCIENCE AND THE EVOLUTION OF PUBLIC POLICY, THE ROCKEFELLER  
UNIVERSITY PRESS, NEW YORK, 1973, P. 31.
- <sup>4</sup>HEALTH, UNITED STATES 1983 AND PREVENTION PROFILE (PREPUBLICATION COPY),  
U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, WASHINGTON, 1983, P. 181.
- <sup>5</sup>VANNEVAR BUSH, SCIENCE AND THE ENDLESS FRONTIER, U.S. GOVERNMENT PRINTING OFFICE,  
WASHINGTON, 1945, P. 8.
- <sup>6</sup>HENRY J. AARON AND WILLIAM B. SCHWARTZ, THE PAINFUL PRESCRIPTION, THE BROOKINGS  
INSTITUTION, WASHINGTON, 1984, P. 37.
- <sup>7</sup>LEWIS THOMAS, "THE MEDICAL LESSONS OF HISTORY," WALL STREET JOURNAL, JULY 3, 1978.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director  
National Institutes of Health

Mr. Chairman, it is my privilege to present the President's budget proposal for the National Institutes of Health (NIH) for Fiscal Year 1987, and to outline briefly our activities and plans. In doing so, I wish to add a personal observation that during the time I have been Director of the National Institutes of Health, I have been impressed by the level of interest and understanding with which you, your colleagues, and the staff of the Subcommittee deal with matters affecting the National Institutes of Health.

Fiscal 1987 will be observed as NIH's centennial year. In August of 1887, the one-room National Laboratory of Hygiene was opened at the Marine Hospital on Staten Island to study cholera and other infectious diseases, hoping that from the research could be found the means for fighting such devastating diseases. Thus began what is described in our centennial slogan as "A Century of Science for Health." For after several changes in name as well as location, the National Laboratory of Hygiene became the National Institutes of Health.

American science in the 1880s was rooted in the work and inspiration of the European giants Robert Koch and Louis Pasteur. It is fortuitous that the centennial of the Pasteur Institute coincides with that of the NIH. In May of the next year, Pasteur and the NIH will hold a symposium on molecular biology in Bethesda as a joint celebration of this important anniversary. Other centennial events are scheduled at various times during the year, including regional salutes to the federal/academic partnership in biomedical research so successfully nurtured by the NIH. These locally sponsored celebrations will be held in such centers of research as Boston, St. Louis, Atlanta, and San Francisco. We see the NIH centennial as much more than an institutional birthday, but rather as an occasion for creating a better understanding among the American people of the importance of biomedical research—an opportunity to convey a sense of its accomplishments and promise.

Among those accomplishments are tremendous advances against acquired immune deficiency syndrome (AIDS). Special attention is being given to involving additional scientific groups and additional AIDS patients in these efforts. The National Cancer Institute and the National Institute of Allergy and Infectious Diseases (NIAID) are planning to fund National Cooperative Drug Discovery Groups, aimed at discovery of effective agents to interfere with replication of the AIDS virus and at restoration or maintenance of the immune response. The NIAID also plans to establish AIDS Treatment Evaluation Units in various locations for the testing of antivirals, immune modulators, and antibiotics in AIDS patients. At the same time, NIH intramural and grant-supported scientists are actively pursuing a variety of scientific approaches to the development of vaccines.



Simultaneously, we are learning a great deal more about the basic structure of the virus itself, how it controls its replication, how it destroys certain target cells. These new insights may prove crucial to the eventual discovery of effective agents for prevention and treatment of AIDS.

The AIDS screening test for donated blood, based on the work of Dr. Robert Gallo of the National Cancer Institute, has provided a means for safeguarding hemophiliacs from AIDS. This test and development of a method for pre-treating Factor VIII against HTLV-III has resulted in a remarkable reduction in risk for hemophiliacs. Studies have shown that in some hemophilia populations over 90 percent of hemophiliacs had developed antibodies to HTLV-III. Several recent studies show that of hemophiliacs who had received only treated Factor VIII, none has developed antibodies to the AIDS-causing virus.

An NCI research team, led by Dr. Steven Rosenberg, has developed a new approach to cancer treatment using interleukin-2 to activate the immune system to destroy cancer cells. The original study in 25 patients has been expanded through funding at 6 medical centers where about 300 additional patients will be treated.

Researchers are making gains against genetic diseases. Recently, NIH scientists, working with investigators elsewhere, found a genetic marker for cystic fibrosis, the most common fatal inherited disease of Caucasians. This discovery permits the identification of most carriers of the disease within families having a history of the disease, and brings scientists closer to finding the gene itself and to discovering the basic defect causing cystic fibrosis. Another major advance has been made in understanding of the genetic neuromuscular disease Duchenne muscular dystrophy (DMD). Scientists have recently cloned a DNA fragment that detects a defect in or near the DMD gene. This work forms the basis for much more accurate detection of female carriers of the gene and for prenatal diagnosis.

Great strides are also being made against the complications of diabetes. Scientists are beginning to understand the role of the enzyme aldose reductase in the development of the cataracts common in diabetes. This research has led to the evaluation of aldose reductase inhibitors--drugs now being tested in clinical trials for the prevention of diabetic eye disease and other complications as well. Research has provided other new treatment options and new hope for the individual at risk for the most serious complications of diabetes. Examples include laser treatment for diabetic retinopathy and improvements in kidney dialysis. Another treatment approach, transplantation of donor pancreas islet cells to replace those lost in diabetes, is progressing with exciting rapidity. Such transplantation of pancreas tissue offers great hope for providing recipients with a close facsimile of the normal function of the pancreas.

As you know, there is growing concern about the rising costs of health care and the impact of biomedical research on these costs. Undeniably, certain fruits of research--especially technological advances--initially may appear to increase health care costs. You will perhaps be interested in an informal survey we

recently conducted at the NIH looking for examples of advances in biomedical research that have reduced health care costs. A selection of just 12 recent advances were estimated to save about \$2.5 billion annually in health care costs. Among these examples were drug treatment rather than surgery for patent ductus arteriosus, a serious heart defect of infants; drug treatment of coronary artery disease instead of coronary bypass surgery in certain patients; and newly developed laser treatment for serious eye diseases.

Mr. Chairman, we understand the need for strong measures to reduce the federal deficit. The budget we present is an example of the kind of restraint the times require of the non-exempt components of the Government. At the same time, we are well aware of the potential impact of the FY 1987 request and will do our best to maintain the stability of the Nation's biomedical research enterprise and the momentum of its recent progress. To do so will require maximum flexibility so that we can make maximum use of our resources to take advantage of scientific opportunities.

Before proceeding to a discussion of the FY 1987 proposal, however, it is necessary to take into account certain adjustments in the FY 1986 budget. The first such modification is a reduction of \$236.2 million, as required by the Balanced Budget and Emergency Deficit Control Act. This 4.3 percent decrease has been applied uniformly against the appropriation of each NIH institute, as well as against each research mechanism at the NIH aggregate level, and each identified program, project or activity. In addition, three rescissions are proposed totaling \$76.8 million in FY 1986 budget authority. These rescissions call for a decrease of \$53.7 million from research project grants as part of a new stabilization policy, a decrease of \$13.9 million appropriated to the Office of the Director for AIDS research, and a decrease of \$9.1 million from the small and minority universities and colleges programs. The reduction in project grants is a necessary transition to the spending levels in the 1987 President's budget. The small and minority schools programs will be continued at the FY 1985 level.

The FY 1987 budget request for NIH is \$4,936,157,000, a decrease of \$131,206,000 or 2.6 percent from \$5,067,363,000 which is the comparable FY 1986 total after deducting for the Balanced Budget Act and the FY 1986 proposed rescissions.

With this presentation of the FY 1987 budget the Administration proposes a new research grant stabilization policy. Under this new policy the total number of NIH research project grants would be stabilized at a total of 18,000 grants. Almost 57 percent of the total proposed NIH budget is allocated for such grants. This is a departure from the previous stabilization policy where the goal was to stabilize the number of competing grants. Thus the FY 1987 request would include support for 18,000 grants of which 5,140 would be competing awards. This compares with 18,357 total grants awarded in FY 1985 and 18,195 such awards projected for FY 1986.

A new method of reimbursing grantees for the indirect cost portion of NIH grant awards is assumed with the FY 1987 budget. This proposal reflects the commonly expressed concerns of both the Congress and the Administration over the escalating costs of research. The new "Fair Share Allocated Overhead Policy" would set



a national maximum limit for academic grantees on the reimbursement rate for the administrative overhead costs that constitute approximately one-half of all indirect cost reimbursements to these institutions. Beginning in FY 1987, the new policy would cap reimbursement for such administration at 20 percent of the grant's direct costs, as compared with the current average of 26 percent for this cost element. Implementation of the new policy is expected to reduce indirect costs by an estimated \$85 million.

The request for \$198.2 million for research training will support about 9,250 predoctoral and postdoctoral trainees--a reduction of 700 trainees from the proposed FY 1986 level of 9,950. The number of research centers in FY 1987 would be decreased by 11 to a total of 523 and the funding for the centers would be reduced by an aggregate of 4 percent from the 1986 funding level.

Other extramural NIH research mechanisms will be maintained at approximately their FY 1986 funding levels. Two exceptions are the Biomedical Research Support Grant (BRSR) Program and the Extramural Facilities Construction Programs, both of which will be eliminated in FY 1987. Because of the continued emphasis on investigator-initiated project grants as the most appropriate form of support, and in the face of growing concern over budget restraints, the BRSR must rank as a lower priority when compared with other NIH programs. The Extramural Facilities Construction Program is also proposed for elimination due to budgetary constraints and the relatively lower priority of this program. Intramural research at the NIH in 1987 would be funded at \$548.4 million, an increase of \$11.5 million or 2 percent above the comparable FY 1986 level.

The FY 1987 budget request for NIH excludes all funding related to acquired immune deficiency syndrome (AIDS). All FY 1987 resources for AIDS are being requested for appropriation to a single account in the Office of the Assistant Secretary for Health (OASH), who will have the responsibility to allocate these funds to the several PHS agencies participating in AIDS research, prevention, and treatment. Estimates of the number of NIH research project grants on AIDS, to be supported from the OASH fund, are included in the numbers of grants counted against the stabilization objective.

In closing, permit me to call attention to the FY 1987 budget proposal for the National Institute for Arthritis, Musculoskeletal and Skin Diseases. Details regarding the planned activities of the new institute will be presented later in the hearings. I believe the committee will also be interested in knowing that the Public Health Service is developing an implementation plan for the establishment of the National Center for Nursing Research at the NIH.

I will be pleased to answer any questions you may have.

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
National Institutes of Health  
1986 Budget Hearings  
Statement of the Director

Once again it is my privilege to present testimony on the President's budget request for the National Institutes of Health. In discussing the proposal for Fiscal Year 1986, I will also touch briefly on the recent progress of biomedical research. It is especially gratifying to report such advances in this setting, Mr. Chairman, because you and the members as well as the staff of the Subcommittee have shown such personal interest in the role of biomedical research in improving the health of the American people. These hearings also provide my associates and me an opportunity to express our thanks to you for your consistent support of the programs of the NIH.

For about 40 years, the NIH has been the principal source of support for the health-related research conducted in America's universities and medical schools, currently supplying almost two-thirds of the funding for such research. The research supported by the NIH, together with that conducted in its own laboratories, has had a profound and beneficial influence on the modern practice of medicine and on the state of health of people throughout the Nation. The vision and persistence of the many who have championed the NIH over the years have been more than amply vindicated.

While the improvement of health is and will continue to be our central purpose, there has been substantial interest of late in a related development, one not foreseen when NIH was established. That is, the beginning of an entirely new industry based on the results of fundamental research for which the Agency was largely responsible. The influence of NIH on biotechnology has been substantial and extensive. A local example of this influence



was reported in a recent article in the Washington Post that credited NIH research with helping to spawn more than 200 biotechnology companies in the Washington area alone. But the influence is international in scope. Recent government and private industry studies attest to the NIH role in fostering this Nation's leadership in biotechnology. The NIH Director's Advisory Committee will devote the entire agenda of its June 1985 meeting to a discussion of that role.

When I appeared before this Committee last year, I expressed our appreciation for your key role in making it possible for NIH to acquire the 11-acre convent property on the western edge of the NIH campus, now designated as the Mary Woodard Lasker Center for Health Research and Education. I am happy to report to you now that because this property was available, the NIH has been able to launch an important new program whose funding comes not from the government but from the private sector. Under an agreement with the Howard Hughes Medical Institute, we are establishing a cooperative program that will afford about 30 students each year an opportunity to engage in research in the course of their medical school training. The students will be chosen in nationwide competition and will spend six months to a year in research training on the NIH campus under the guidance of leading NIH scientists. The Hughes Institute will support this program at a cost of about \$10.5 million for the first five years. Recruitment began last fall with the first group of students to enter the program in the fall of 1985. A gratifying number of first-rate students applied.

We are convinced that this kind of early exposure to research is an important factor in attracting bright and dedicated medical students into biomedical research. Much of today's most challenging research requires individuals who are both medically knowledgeable and scientifically trained.

In commenting on the essential relationship existing between the conduct of research by the NIH and the practice of medicine, I should take note of two events of the past year that are symbolic of an increasing awareness of such ties.

A special issue of the Journal of the American Medical Association, last October, devoted almost 50 pages to descriptions of the entire range of activities of the NIH to tell, in the words of the news editor, "what the existence of the NIH means for the practice of medicine."

In January 1985, another widely circulated publication, Medical World News, devoted much of its 25th anniversary issue to the National Institutes of Health. In the lead editorial, the comment was made that "few of the mainstays of clinical practice today have not had their origins in NIH research . . ."

Communication with both the health care and the biomedical research communities, making full use of advanced technology, continues to be an important function of the NIH's National Library of Medicine.

Briefly, I will mention a few of the highlights of research accomplishments by scientists working in or supported by the various components of the NIH:

- o There has been important progress on acquired immune deficiency syndrome (AIDS), particularly from the NIH laboratory of Dr. Robert Gallo. Dr. Gallo and French scientists independently discovered a virus that is the causative agent of the disease. More recently,

the entire genetic structure of the virus has been mapped. This opens the way for new treatment opportunities and prevention strategies and will accelerate work aimed at vaccine development. Moreover, Dr. Gallo's method for detecting the AIDS virus antibody has led to the development of commercial test kits to screen blood and thus protect the Nation's blood supply.

- o NIH intramural scientists, also using genetic engineering techniques, have cloned the entire gene for the major antigen on one life cycle stage of the human malaria parasite Plasmodium falciparum. This discovery will allow preparation of sufficiently large quantities of the antigen to test for its potential use in a vaccine. Malaria is an important and growing world problem, due to increasing numbers of drug-resistant parasites and insecticide-resistant mosquitoes that are overwhelming ongoing control efforts.
- o A study supported by NIH at several centers has shown that clots in blood vessels of the heart can be dissolved by administration of an agent rt-PA (tissue-type plasminogen activator) in patients developing heart attacks. This trial confirms that the agent can re-open blocked vessels quickly and probably without some of the side effects of other clot-dissolving agents. The treatment, with further study, may represent a major advance in the care of the 680,000 patients annually who experience a blood clot in the coronary vessels.
- o NIH intramural scientists have succeeded in developing a vaccine that promises to be effective against herpes simplex virus--the virus that causes "cold sores" or "fever blisters" on the skin or mucous membranes.

The researchers used a technique developed at NIH--whereby herpes virus proteins are inserted into Vaccinia virus to produce a recombinant or hybrid virus. The genetic material of hepatitis B, of rabies, and of almost any organism can be inserted into Vaccinia virus. For rabies, influenza, and hepatitis B, very good protection can be induced in experimental animals.

- o In another clinical advance, NIH intramural scientists have found that the drug cyclosporine can rapidly reduce eye inflammation in patients with posterior uveitis, a serious disease that can severely limit vision. In most cases, vision also improved with control of inflammation.

Scientists at NIH and others supported by NIH grants continue to discover more potential cancer-causing genes (oncogenes) and "map" their locations on human chromosomes. Such studies continue to confirm the role of these oncogenes in the origins of cancer. Further study may reveal ways to destroy or block the products of these oncogenes, and result in advances in cancer prevention, diagnosis and treatment.

The directors of the constituent bureaus, institutes, and divisions of NIH will present further information about accomplishments in their respective areas of responsibility. They also will outline their program plans for the coming year in the light of the President's budget. I will confine my comments on the budget to matters that affect the NIH as a whole, addressing particularly the novel features of this year's proposal.

The basis for development of the Fiscal Year 1986 budget for the NIH is the Administration's policy essentially to freeze domestic programs at the



1985 funding level. To accomplish this purpose without upsetting the stability of our major research support program requires adjustments in FY 1985 spending with regard primarily to the funding of research grants.

Research project grants to individual investigators continue to receive the highest priority because they support the primary source from which fundamental discoveries emerge. Thus they represent the key mechanism in Federal support of biomedical research. The 1985 budget will fund 5,000 new and competing renewal research project grants and approximately 12,172 continuation awards arising from competition in previous years. About 646 of the 5,000 new and competing renewal awards will receive funding in 1985 for three years of support. This multiyear funding policy is intended to avoid significant fluctuations in the number of grants NIH is able to support and to lower future noncompeting requirements.

The 1985 budget also includes \$482,144,000 for 500 research centers. This represents an increase of four centers over 1984 and includes support for three new research centers on Alzheimer's disease and related disorders. As with research project grants, some of the research centers will receive multiyear support. Approximately 45 of the 500 centers will be awarded two years of support from FY 1985 funds.

Turning now to the 1986 budget, the request for NIH is \$4,852,680,000, a decrease of \$282,048,000 from the comparable 1985 level. Examined from a program level perspective, however, the request represents close to a 2 percent increase over 1985. This increase reflects the 1986 budget authority, plus the second year resources provided from 1985 funds. The budget request will support 12,957 full-time equivalent staff positions,

a reduction of 150 from the 1985 level of 13,107, and a reduction of 704 from the 1984 actual usage of 13,661. The budget also assumes savings of \$29.8 million in administrative costs and \$19.1 million as the result of the proposed 5 percent reduction in pay costs.

The request supports an estimated 5,900 new and competing renewal research project grants and 11,242 noncompeting (i.e., previously competed) research project grants. Including the estimated 646 grants which were multiyear funded in 1985, the total number of active research project grants in 1986 will be 16,888. Direct costs of research project grants in 1986 will be funded on the average at the historical levels of 97 percent of costs recommended by study sections for new and competing renewal awards, and 99 percent of committed amounts for noncompeting awards. The NIH aggregate average costs will be approximately 6.0 percent higher than 1985 for new and competing renewal awards, and about 7.8 percent higher for noncompeting continuations.

The 1986 request includes \$412,391,000 to fund 455 research centers. The 45 centers that were multiyear funded in 1985 will remain active in 1986, thus a total of 500 centers will be ongoing in 1986, the same number as will be supported in 1985. The budget assumes the same average costs in 1986 as in 1985.

As part of the Administration's effort to hold domestic programs at the 1985 level, indirect costs rates associated with research grants will be held at the 1985 rate. It is estimated that this measure will save about \$23 million.

NIH will support approximately 9,900 research trainees in 1986; the same number is estimated to be supported in 1985. This represents about 94 percent of the level recommended by the National Academy of Sciences for the NIH. Consistent with the overall freeze guidance, stipend levels are maintained at their 1985 level which represents an increase over 1984.

Budget authority of \$561,653,000 is requested for intramural research in 1986. The decrease of \$17,638,000 from the 1985 level represents the savings resulting from government-wide reduction in administrative costs and the proposed 5 percent paycut.

In summary, the 1986 request for the NIH represents a realistic level of Federal support for biomedical research and research training in the context of the rising Federal deficit and the need for Federal fiscal austerity. The 1986 request reflects the Administration's commitment even in times of scarce resources to a stable program of biomedical research and research training.

I will be pleased to answer any questions you may have.

REMARKS

PRESENTATION LUNCHEON FOR THE WOMEN IN SCIENCE AND  
ENGINEERING (WISE) AWARD  
WESTPARK HOTEL, ROSSLYN, VIRGINIA  
MARCH 24, 1986

JAMES B. WYNGAARDEN, M.D.

IT IS A PLEASURE FOR ME TO JOIN WITH ALL OF YOU IN SALUTING TODAY'S HONOREES. I WAS HONORED TO HAVE BEEN ASKED BY DR. OTIS R. BOWEN, THE SECRETARY OF HEALTH AND HUMAN SERVICES, TO REPRESENT HIM ON THIS OCCASION AND TO EXPRESS HIS REGRET THAT IT WAS NOT POSSIBLE FOR HIM TO ATTEND. DR. BOWEN ALSO ASKED ME TO TELL YOU OF THE PRIDE AND PLEASURE HE FELT ON BEHALF OF THE DEPARTMENT ON LEARNING OF THE AWARD TO DR. NAOMI LYNN GERBER. BECAUSE DR. GERBER IS A VITAL MEMBER OF THE STAFF OF THE NATIONAL INSTITUTES OF HEALTH, I TOO TAKE GREAT PLEASURE IN CONGRATULATING HER ON THE HONOR SHE IS RECEIVING TODAY. I WISH ALSO TO EXPRESS TO THE INTERAGENCY COMMITTEE OUR GRATITUDE FOR THE RECOGNITION BEING GIVEN TO ONE OF OUR VALUED COLLEAGUES.

DR. GERBER'S ACHIEVEMENTS EXTEND ACROSS THE RANGE OF COMPLEMENTARY FUNCTIONS THAT HAVE BECOME THE TRADITIONAL THREEFOLD OBJECTIVES OF OUR GREAT MEDICAL CENTERS. SHE HAS MADE SUBSTANTIAL CONTRIBUTIONS NOT ONLY TO RESEARCH, BUT ALSO TO EDUCATION AND CLINICAL CARE IN THE FIELD OF PHYSICAL REHABILITATION. IN A UNIQUE WAY HER CAREER AT NIH IS A BALANCED EXPRESSION OF THE DEPTH AND SCOPE OF OUR CONCERNS.



I AM GLAD FOR THE OPPORTUNITY TO LEARN MORE OF THE ACTIVITIES OF THE INTERAGENCY COMMITTEE ON SCIENCE AND ENGINEERING. THROUGH THE RECOGNITION OF EXCELLENCE YOU PROMOTE EXCELLENCE AND MAKE KNOWN THE RANGE OF OPPORTUNITIES OPEN TO WOMEN IN SCIENCE AND ENGINEERING-- ESPECIALLY IN GOVERNMENT SERVICE.

THANK YOU.

# THE NATIONAL INSTITUTES OF HEALTH AT THE CROSSROADS\*

by

James B. Wyngaarden, M.D.\*\*

Essentially all of the issues, challenges and opportunities that have been discussed during this 33rd Annual Health Forum bear directly on the National Institutes of Health (NIH). I am pleased to have an opportunity to comment on many of these matters in the light of the presentations and dialogue of the past two days.

Without discounting in any way the current problems and foreseeable difficulties, I continue to be an optimist about the future of the National Institutes of Health. More than most, I suspect, I am aware of the funding crunch but, despite current fiscal pressures, it is my conviction that the road ahead for NIH does not lead to disaster. I base this belief on the fact that the commitment of the Federal Government to the support of biomedical research designed to improve human health is strong and steady in both the Executive and Legislative Branches.

The current fiscal situation brings to mind the time a little less than 20 years ago when, after a long period of sustained and rapid growth from year to year, the NIH appropriation took a step backward. In 1953 the total NIH appropriation was about \$60 million, by 1957 it was more than triple that amount. The 1957 appropriation was doubled by 1960, and this amount had been tripled by 1967. But the Viet Nam war had its effect so that the appropriation of approximately \$1.2 billion in 1968 was \$234 million less than it had been the previous year, a reduction of more than 16 percent. This was a shocking event and some elder statesmen in science saw the reduction as "the beginning of the end in Federal support of biomedical research."

The year 1968 was an inflection point in the growth curve of the NIH appropriation. For the proceeding 20 years the NIH appropriation had grown in purchasing power at an average rate of 24 percent per year. But from 1968 to the present the real growth has averaged about 2 percent per year. Rather than the "beginning of the end," however, the 1967-68 event could more accurately be characterized in Winston Churchill's inversion of the familiar phrase. The pause in the NIH budget marked the inevitable "end of the beginning."

---

\*Address presented at the 33rd National Health Forum,  
March 25, 1986, Washington, D.C.

\*\*Director, National Institutes of Health, Bethesda, Maryland

Now, in 1986, it is instructive to review what has happened, what steps have been taken, and what the effects of the sea change have been.

The primary challenge has been to maximize scientific productivity in the face of budgetary limitations. The response has been a continuing series of adjustments in the Agency's programs and activities. Such adjustments inevitably translate to hard choices as to priority among competing programs and extend to the difficult choices that must be made between individual grant proposals at the project level. In this latter category, choices among meritorious project proposals have become increasingly difficult because the numbers of biomedical scientists and grant applications have grown faster than the NIH budget.

Since 1974 we have annually shifted funds into the research grant category from contracts and other mechanisms to fund more investigator-initiated projects. In the FY 1987 appropriation request, project grants amount to almost 57 percent of the total NIH budget. As recently as 1980 the share of our total budget going to project grants was more than 10 percentage points lower. During the early 1970s the share of the NIH budget devoted to project grants was consistently less than 40 percent.

As a result of the shift in funds to favor the project grant mechanism, our research grant portfolio has grown from about 10,000 in 1970 to the current total of more than 18,000. And this increase in numbers of grants has occurred during a period when the average cost per grant per year has grown from about \$35,000 to the amount of \$147,000 reached in Fiscal Year 1985.

At a time when the number of grants awarded has essentially doubled, the proportion of the meritorious applications we have been able to fund has declined to an estimated award rate of just over 30 percent in the current fiscal year (after GM and Rescission). As a consequence of the steady decline in the award rate, there has been heightened anxiety among the scientists about the funding of their research and concern about the equity of the peer review system itself.

The current constraints on funding for projects and maintenance of necessary infrastructure are real, but there is considerable misunderstanding within the scientific community about the causes and about the adjustments that we have made to minimize the effects of the tightened budgets. In this context I believe it is useful to address some of the features of the appropriation requests now being considered by the Congress.

A major portion of the fiscal 1987 request, the amount for project grants, was based on a new criterion for the so-called stabilization initiative, defining the minimum as 18,000 total grants instead of the previous landmark of 5,000 new and competing awards. This does not make a significant change in the likelihood of funding of any individual proposal in any given year, and is probably more manageable. I am encouraged to note that the level of 18,000 grants, recommended in an otherwise spare President's budget, is very near the all time high in research project grants (18,249) that was reached in Fiscal Year 1985. On the other hand, it appears that it will be necessary under the proposal to negotiate the amounts of existing and new grants downward to maintain the 18,000 total.



In constructing the 1987 budget, we were required to make a number of unwelcome choices in program priorities in order to stay within the permitted total levels. As previously, we opted to do everything possible to protect funding for investigator-initiated grants. The amounts necessary to maintain our commitment to project grants required that 57 percent of our Fiscal Year 87 budget be devoted to project grants.

The priority accorded project research in combination with the tightened overall budget forced further reduction in certain categories of research funds that grantees can administer with a degree of flexibility--for example, the stringencies of the FY 87 budget require elimination of biomedical research support grants. The FY 1987 adjustments also made it necessary to eliminate extramural construction grants and to place a cap on a major component of indirect costs so as to lower the total.

In recent years, when budgets have been especially tight, we have been asked if the NIH intramural program is subjected to the same rigorous restraints as the extramural. The answer is yes. From year to year the increases may differ, favoring first one and then the other, but their growth has been almost exactly the same if comparisons are made on a multiyear basis. For example, the growth in the extramural budget between 1977 and 1985 was 114 percent; in the same period the intramural budget grew by 111 percent.

One area of special concern for the present as well as the future is research training, where the number of slots has been reduced by 1,200 over the past two years. We are attempting to reduce the impact of the cuts in training by giving special emphasis to the programs that have been most productive in scientists who can compete successfully for research funds. While the recent reductions in trainee slots signal a problem, we cannot regard training as simply a numbers game. The bottom line is the quantity and quality of training and the product that comes out of the training.

The current situation adds urgency to our perception of the need to look carefully at our training programs, the full array of them, and the task deserves substantial study. Some of our postdoctoral training programs training primarily M.D.s, as clinicians-scientists, are no doubt very productive; others clearly have not been so effective. This may vary by field, it may vary within the same field by institution, it may vary within the same institution by policies in one division compared with another. On the basis of inquiry, however, we should be able to select characteristics of training programs that tend toward success. We have a clear and present responsibility to make the most of a reduced number of training slots.

In a current effort to enhance research training for M.D.s, NIH is attempting to make training grants to clinical departments more efficient. We will soon advise all program directors that we are reemphasizing certain elements of the guidelines to enforce our conviction that all postdoctoral trainee physicians need longer periods of training. We would like all such trainees to commit themselves to a minimum of two years of research training, of which not less than 80 percent of the time is devoted to research. In addition, we also stress a stronger basic science component. As a result, it is hoped that M.D. trainees will become more successful competitors for research grants.



Properly so, this forum has included a session on the use of animals in research. It is obvious that serious attention must be given by all of us to the issues that have been raised by the so-called animal rights groups. As you probably know, NIH is conducting what amounts to a comprehensive review of the use of animals in all its funded programs through the screening of new assurances of compliance with the new animal use guidelines required of all of our supported extramural institutions. We also are intensifying and augmenting peer review of intramural and extramural proposals involving animal subjects. Such review is to consider not only the scientific merit but also the feasibility and the propriety of the use of the kinds and numbers of animals in the various protocols. We are also endeavoring to sensitize program personnel and reviewers to the sometimes overlooked but important factor of "social acceptability" of proposed research.

Although we did not make plans to that end, NIH funded research has spawned new economically significant technologies. We have taken responsibility to assure safe, orderly development of such advances as recombinant DNA. Because of the substantial economic impact realized and clearly promised by the new technologies, it has been suggested that consideration be given in our program priorities to put more emphasis on research with economic potential. However, we have reaffirmed our policy position that NIH can serve best by doing what it does the best--conducting and supporting excellent biomedical science.

In the face of all the complexities that have proliferated as the NIH has grown and times have changed, I am optimistic about the future. By singling out the 1967-68 pause in growth as a unique event, I am at the same time taking note of the fact that there have been no steps backward in current dollars since that time, and year to year reductions in constant dollars have been rare and minor in amount. Having just been through the budget development process within the Administration and defense of budget in the congressional appropriations hearings, I am aware of and heartened by the support of strong champions of NIH within the Executive and Legislative Branches.

These champions within the Government, as well as our many strong advocates outside the Government, act on their conviction about the incalculable long-term value of research, and because their support is so firmly based we can have confidence in their constancy.

Even the Heritage Foundation, not noted for encouraging Federal expenditures, sounded the same fundamental note that has motivated the establishment and growth of NIH. In a proposal by the staff of the Heritage Foundation for the FY 1987 Federal budget, titled "Slashing the Deficit," the programs of many agencies are examined in detail.

In the discussion of the NIH budget, and before adding a cautionary note as to how NIH might allocate funds more judiciously, the Heritage Foundation staff commented, "Basic biomedical research is one of the few activities funded through Washington which is appropriately a Federal responsibility." The writer went on to declare, "Historically, the benefits of such research have outstripped the taxpayers costs."<sup>1</sup> I could not have said it better.

If you have questions, I'll be glad to respond to them.

202

Reference

<sup>1</sup>"Slashing the Deficit", a proposal by the Staff of the Heritage Foundation.  
The Heritage Foundation, Washington, D.C., 1986, p. 90



203

**WELCOMING REMARKS\***

by

James B. Wyngaarden, M.D.\*\*

I want to welcome you to the 1986 Savings Bond Campaign.

As the Coordinators and Canvassers for this worthwhile effort, the success of this campaign will depend on you. Over the years NIH has been an active participant in the Department's Savings Bond effort and I look forward to another successful campaign.

I cannot overstress the value of systematic savings through the payroll savings plan, and I am sure that you agree. Since we know that the product is sound, we must look then to our approach to getting the message across to our varied NIH population. Your training today will provide the technical foundation for conducting a successful Bond Campaign. However, what is needed, as much as the information you will impart to your colleagues, is a sense of enthusiasm for the product you are providing.

I have been assured that the Bond Drive will be only for one month, April 2 thru May 2, and I ask that you give full effort to making this campaign a success. Take the time to talk personally with each of your assigned staff. If you sign them up for Savings Bonds today, they will thank you tomorrow.

Our goal is to increase participation by at least 15% this year. This objective can easily be achieved if we inform all segments of NIH personnel of the value of bonds as an investment to help accomplish this. We are taking several steps: first, Under Secretary Newman will be visiting with the Scientific Directors on April 16 to lend his effort to gaining their enthusiastic support; second, we will provide solid, sensible information and a minimum of "hoopla"; and third, we have arranged for some unusual incentives for participation that you will be hearing about shortly. In addition, I will speak with the BID Directors to encourage their support for your efforts.

Secretary Bowen and I appreciate your help in getting the word out. I know you will be learning a great deal today that will be very helpful to you. My purpose here is to thank you in advance.

Have a good campaign!

---

\* The 1986 Savings Bond Campaign Training Meeting for Canvassers and Coordinators on March 31 in Building 1, Wilson Hall.

\*\* Director, National Institutes of Health, Bethesda, Maryland.





304

REMARKS FOR JAMES R. WYNGAARDEN  
NIH CENTENNIAL COMMITTEE DINNER AT THE SKY CLUB  
APRIL 2, 1986

MANY PEOPLE FIND IT HARD TO IMAGINE THAT THE NIH IS APPROACHING A CENTURY. MOST DATE OUR BEGINNING AT SOMETIME AROUND WORLD WAR II, SO I WILL GIVE YOU A BRIEF CHRONOLOGY. THE NIH BEGAN IN 1887 AS THE "HYGIENIC LABORATORY", A ONE-ROOM FACILITY IN THE MARINE HEALTH SERVICE HOSPITAL ON STATEN ISLAND. THE SOLE RESEARCHER WAS DR. JOSEPH KINYOUN, A PHYSICIAN AND BACTERIOLOGIST WHO STUDIED IN THE LABS OF PASTEUR AND KOCH.

THE HYGIENIC LABORATORY MOVED TO WASHINGTON IN 1891, RESIDING FIRST IN THE BUTLER BUILDING ADJACENT TO THE CAPITOL. IN 1904 THE LABORATORY MOVED TO 25TH AND E STREETS, N.W. DURING THE FIRST 25 YEARS OF ITS OPERATION, THE LABORATORY CONCENTRATED ITS RESEARCH ACTIVITIES ON INFECTIOUS DISEASES. THE PANSDELL ACT OF 1930 CHANGED THE NAME OF THE HYGIENIC LABORATORY TO THE NATIONAL INSTITUTE OF HEALTH AND ASSIGNED THE NIH THE BROAD MISSION OF "ASCERTAINING THE CAUSE, PREVENTION, AND CURE OF DISEASE."

MR. AND MRS. LUKE WILSON DONATED THE FIRST PARCEL OF THEIR BETHESDA ESTATE "TREE TOPS" AS THE FUTURE SITE OF THE NIH IN 1935. THE CORNERSTONE FOR BUILDING ONE WAS LAID JUNE 30, 1938. IN 1948, THE PLURAL NATIONAL INSTITUTES OF HEALTH CAME INTO BEING, MERGING THE PRE-EXISTING NATIONAL CANCER INSTITUTE WITH THE NEWLY MANDATED NATIONAL HEART INSTITUTE. EVENTUALLY SOME 40 BUILDINGS WERE ERECTED ON THE BETHESDA "CAMPUS", WHICH GREW FROM THE WILSON'S 92-ACRE GIFT TO ENCOMPASS OVER 300 ACRES.

THE 912 NIH EMPLOYEES WHO CAME TO BETHESDA IN 1938 HAS INCREASED TO MORE THAN 14,000 IN 1986.

PRIOR TO WORLD WAR II, MOST BIOMEDICAL RESEARCH IN THE U.S. WAS SUPPORTED BY PRIVATE INDUSTRY OR ACADEMIC INSTITUTIONS. AFTER THE WAR, THE ONGOING HEALTH RESEARCH PROJECTS SUPPORTED AT UNIVERSITIES AND HOSPITALS BY THE WARTIME OFFICE OF SCIENTIFIC RESEARCH AND DEVELOPMENT WERE RE-ASSIGNED TO THE NIH. FROM THIS NUCLEUS OF LESS THAN ONE MILLION DOLLARS IN GRANTS AND CONTRACTS, THE NIH'S EXTRAMURAL PROGRAM HAS GROWN TO OVER \$4 BILLION, WHICH REPRESENTS ABOUT 80 PERCENT OF THE TOTAL 1986 BUDGET. NIH CURRENTLY FUNDS OVER 20,000 RESEARCH GRANTS ANNUALLY. TODAY, NINETY PERCENT OF THE BASIC BIOMEDICAL RESEARCH DONE IN THIS COUNTRY IS SUPPORTED BY THE NIH, AND SOME SIXTY PERCENT OF ALL FEDERALLY SUPPORTED HEALTH RESEARCH IS CONDUCTED BY THE NIH.

IN MY RECENT TESTIMONY BEFORE THE APPROPRIATIONS SUBCOMMITTEE, SENATOR WEICKER CONFIRMED WHAT WAS ALREADY OUR PRIMARY ORIENTATION IN CELEBRATING THE NIH CENTENNIAL. HE SPECIFICALLY ASKED WHAT THE PLANS WERE FOR THE PUBLIC CELEBRATION OF THE NIH'S 100TH ANNIVERSARY "TO TELL THE AMERICAN PEOPLE WHAT A JEWEL THEY HAVE IN THE NIH." WHAT FOLLOWS IS A SUMMARY DESCRIPTION OF THOSE ACTIVITIES.

LET ME STATE AT THE OUTSET THE TWO PRIMARY OBJECTIVES IN A CENTURY OF SCIENCE FOR HEALTH:

FIRST, WE WANT TO ENLIGHTEN AND EDUCATE THE PUBLIC ABOUT THE WORTH AND BENEFIT OF WHAT WE DO. BY WE, I MEAN ALL OF THE PARTNERS IN BIOMEDICAL RESEARCH - ACADEMIA, INDUSTRY, THE PUBLIC SECTOR AND VARIOUS ALLIED INSTITUTIONS SUCH AS THE HOWARD HUGHES MEDICAL INSTITUTE. WE HAVE SINGLY AND COLLECTIVELY COME IN FOR MORE THAN OUR SHARE OF CRITICISM RECENTLY - THE CONCERNS WITH THE USE OF ANIMALS IN RESEARCH TO GIVE BUT ONE EXAMPLE. THESE CONCERNS ARE RAISED BY A PUBLIC THAT HAS FORGOTTEN OR NEVER KNEW WHAT THE WORLD WAS LIKE BEFORE THE ADVANCES OF MODERN MEDICINE. THE YEAR OF 1887 IS A LONG WAY AWAY, WITH ITS PLAGUES AND PESTS. WE NEED TO REMIND THE PUBLIC OF HOW FAR WE HAVE COME.

SECONDLY, WE WANT TO ATTRACT MORE YOUNG, BRIGHT PEOPLE INTO THE ADVENTURE THAT IS BIOMEDICAL RESEARCH. WE HAVE JUST BEGUN TO REALIZE THE AWESOME POTENTIAL OF MODERN RESEARCH TECHNIQUES, BUT WE NEED TO REMIND PARTICULARLY THE YOUNG PUBLIC OF HOW FAR WE HAVE TO GO. HERE ARE SOME OF THE WAYS WE HOPE TO ACCOMPLISH THIS:

\*THE PRIMARY PUBLIC EVENT IS THE PUBLIC TELEVISION SERIES THAT YOU WILL HEAR MUCH MORE ABOUT VERY SHORTLY. THOUGH THE NIH CENTENNIAL IS THE PROXIMATE CAUSE OF THIS SERIES, THE INTENT IS TO TELL THE STORY OF THE PARTNERSHIP OF ACADEMIA, INDUSTRY, AND PUBLICLY SUPPORTED RESEARCH THAT BROUGHT ABOUT THIS REVOLUTIONARY CENTURY IN THE BIOMEDICAL SCIENCES. IT IS A UNIQUELY AMERICAN STORY, BUT ONE WHICH ENCOMPASSES THE ENTIRE GLOBE IN ITS QUEST "TO IMPROVE THE HEALTH OF ALL MANKIND."



\*A MAJOR PUBLICATION WHICH TRACES THE SAME THEMES AND TELLS THE SAME STORY IN GREATER PICTORIAL AND TEXTUAL DETAIL IS ALSO PLANNED. IT WILL LINGER ON COFFEE TABLES AROUND THE COUNTRY AS AN EVOCATIVE REMINDER. IT AND THE TV SHOWS WILL HOPEFULLY BE ACCOMPANIED BY ANCILLARY EDUCATIONAL MATERIALS FOR USE IN HIGH SCHOOL AND COLLEGE SCIENCE CLASSES.

\*A TRAVELLING EXHIBIT ALSO BASED ON THE SAME THEME COULD BE SENT TO THE MAJOR SCIENCE MUSEUMS AND LEARNING CENTERS THROUGHOUT THE COUNTRY. IN ADDITION WE HAVE ARRANGED WITH THE SMITHSONIAN INSTITUTION TO HAVE A "CASE OF THE MONTH" ON THE MAIN EXHIBIT FLOOR OF THE NATIONAL MUSEUM OF AMERICAN HISTORY AND ALSO HOPE TO HAVE A YEAR-LONG DISPLAY IN THAT MUSEUM'S HALL OF MEDICINE. KINYOUN'S ORIGINAL MICROSCOPE WILL BE LOANED TO US BY THE SMITHSONIAN AND ON DISPLAY IN NIH'S VISITOR INFORMATION CENTER, TOGETHER WITH A VIAL OF DIPHTHERIA ANTITOXIN LABELLED "HYGIENIC LABORATORY - 1893".

\*THE CENTENNIAL OFFERS A UNIQUE OPPORTUNITY AS A "NEWS PEG" FOR FEATURE ARTICLES IN A WIDE VARIETY OF MEDIA. IN FACT, THE MAY ISSUE OF LADIES HOME JOURNAL AND THE OCTOBER 1986 ISSUE OF GOOD HOUSEKEEPING WILL CARRY ARTICLES WHICH TAKE THAT PERSPECTIVE. WE WILL PROMOTE FURTHER FEATURE PLACEMENT AS THE CENTENNIAL YEAR BEGINS.

\*WE WILL ALSO HOLD A PUBLIC OPEN HOUSE ON THE NIH CAMPUS WITH LAYORIENTED EXHIBITS AND PRESENTATIONS. THE THEME FOR THESE ACTIVITIES WILL BE "THEN AND NOW" SOMEWHAT SIMILAR TO THE "SAMPLER" BOOKLET THAT EACH OF YOU WILL RECEIVE. THE LAST SUCH OPEN HOUSE WE HELD ATTRACTED SOME 40,000 VISITORS, INCLUDING MANY MEMBERS OF CONGRESS AND THEIR FAMILIES.

\*EIGHTY PERCENT OF NIH IS EXTRAMURAL, AND WE HOPE TO TRULY MAKE THIS A NATIONAL CELEBRATION BY PROMOTING REGIONAL CELEBRATIONS OF THE NIH CENTENNIAL. ALREADY, A GROUP HAS SPONTANEOUSLY FORMED IN BOSTON, AND GREAT INTEREST IS EVIDENCED IN ST. LOUIS, ATLANTA, SAN FRANCISCO AND ELSEWHERE.

\*NIH IS ALSO AN INTERNATIONAL AGENCY, AND, IN FACT, WE SHARE THIS 1987 CENTENNIAL WITH THE PASTEUR INSTITUTE. WE WILL BE CELEBRATING WITH THEM AT A JOINT SYMPOSIUM IN MAY OF '87. AN INTERNATIONAL SALUTE IS ALSO LINKED TO THE MEETING OF THE EUROPEAN MEDICAL RESEARCH COUNCIL TO BE HELD IN WASHINGTON IN JUNE OF '87. THAT MEETING WAS TO BE HELD IN DUBLIN, BUT WAS MOVED TO WASHINGTON WHEN THE EMRC LEARNED OF THE IMPENDING ANNIVERSARY.

\*1987 IS THE BICENTENNIAL OF THE US CONSTITUTION, AND WE ARE IN DISCUSSION WITH THE CHIEF JUSTICE BURGER'S STAFF AS TO HOW WE CAN JOINTLY ACKNOWLEDGE OUR SHARED ANNIVERSARY. SEPTEMBER 17, 1987 WILL BE A NATIONAL HOLIDAY IN HONOR OF THE CONSTITUTION.

\*1987 ALSO MARKS THE CONVENING OF THE 100TH CONGRESS, A CENTENNIAL WE PLAN TO SHARE BOTH THROUGH PARTICIPATION OF THE CONGRESSIONAL MEMBERS IN THE REGIONAL CELEBRATIONS AND IN THE HOSTING OF A RECEPTION ON CAPITOL HILL FOR THE 60 LIVING NIH NOBEL LAUREATES.

\*DR. FREDRICKSON ALSO HAS ASKED THE PRESIDENT TO HOST A DINNER OR RECEPTION OF THESE SAME NOBELISTS IN A GESTURE SIMILAR TO THE DINNER PRESIDENT KENNEDY HELD FOR THE AMERICAN NOBELISTS IN 1963. PRELIMINARY INDICATIONS FROM THE WHITE HOUSE ARE POSITIVE.

\*WE WILL BE CONDUCTING THE CENTENNIAL YEAR AT NIH FROM OCTOBER OF 1986 TO OCTOBER OF 1987. EACH OF THE 12 INSTITUTES WILL HAVE A PARTICULAR MONTH IN WHICH TO CONDUCT CENTENNIAL RELATED ACTIVITIES WITH ITS GRANTEE INSTITUTIONS, WITH THE EMPHASIS ON PUBLIC EDUCATION PROGRAMS.

\*THE CULMINATION OF THE NIH CENTENNIAL WILL BE OCTOBER 16 THROUGH OCTOBER 19 IN 1987. THAT FRIDAY WILL SEE THE DEDICATION CEREMONY HELD ON THE NIH CAMPUS WITH SUITABLE LUMINARIES, AGAIN PERHAPS INCLUDING THE PRESIDENT, IN ATTENDANCE. FRAMING THAT EVENT WILL BE SCIENTIFIC SYMPOSIA HELD AT THE VARIOUS NIH AUDITORIA. SATURDAY AN ALL-DAY PLENARY SCIENTIFIC SYMPOSIA WILL BE HELD IN THE KENNEDY CENTER FOR THE RETURNING NIH ALUMNI AND FRIENDS, AND THAT EVENING WE WILL HOLD A DINNER DANCE IN THE PENSION BUILDING, A MAGNIFICENT STRUCTURE COMPLETED IN 1887 THAT HAS BEEN THE SITE OF SEVERAL INAUGURAL BALLS.

SUNDAY WILL BE A BRUNCH ON THE NIH CAMPUS AND "LAB PARTIES" FOR THE ALUMNI AND FRIENDS TO SAY FAREWELL.

I WOULD LIKE TO PERSONALLY EXTEND MY INVITATION TO EACH OF YOU TO ATTEND THAT CELEBRATORY WEEKEND. I INVITE YOU NOT JUST AS FRIENDS, BUT AS PARTNERS OF THE NIH IN CELEBRATING THIS EXTRAORDINARY CENTURY OF ACHIEVEMENT. I HOPE THAT TOGETHER WE CAN TELL THE AMERICAN PUBLIC AND THE WORLD ABOUT WHAT THIS PARTNERSHIP HAS ACCOMPLISHED AND CAN ACCOMPLISH. I NOW TURN THE PROCEEDINGS OVER TO MY GOOD FRIEND, DON FREDRICKSON, WHO IS CHAIR OF THE NIH CENTENNIAL COMMITTEE.





CLINICAL INVESTIGATION: NIH PERSPECTIVE\*

by

James B. Wyngaarden, M.D.\*\*

I am very happy to join you this evening during this conference devoted to clinical investigation.

As you know, the mission of the National Institutes of Health is to support and conduct a broad range of research activities aimed at the acquisition of fundamental knowledge and the testing and evaluation of biomedical agents and practices. The boundaries delineating our research mission exclude health care delivery, but are somewhat porous and permit some activities aimed at moving the fruits of research toward application in the community setting. We recognize Congressional intent in naming the institution the National Institutes of Health, not the National Institutes of Science, and that clinical investigators have major contributions to make in the discovery of fundamental new knowledge as well as in the transfer of technology into practice.

There is no doubt in my mind that the pathway to discovery moves not only from bench to the bedside but also from bed to bench. The role of the clinical investigator becomes increasingly critical as the biological revolution spawned some forty years ago, largely through NIH support

---

\*Address given at the Second National Conference on Research Goals and Methods for Otolaryngology-Head and Neck Surgery, April 4, 1986, Washington, D.C.

\*\*Director, National Institutes of Health, Bethesda, Maryland

for basic laboratory research, is beginning to approach major questions with immediate relevance to human health. Because many of the understandings gained from the age of molecular biology are now beginning to move toward clinical application, it is obvious that we will need a steady supply of well-trained physician-scientists to help in the incorporation of this new knowledge into the working motifs of medicine. It is also critical that we have a sufficient supply of clinical scientists able to make observations in the patient setting, to formulate them as solvable scientific questions, and research them using modern scientific techniques and methods. Examples of this type of research come readily to mind--Aaron Lerner's explanation of the biology of benign and malignant pigment cells, for example, and the elucidation of the LDL pathway of cholesterol metabolism by Nobelists Brown and Goldstein. In this type of research, the clinical question is the central force of the investigation. It is a most exciting type of research, requiring someone who is both medically knowledgeable and scientifically trained.

It is for these reasons that, even before I came to NIH as Director in 1982, I was concerned about the decrease in the participation of M.D.'s in research. While the number of M.D.'s participating in NIH supported research as principal investigators has remained about the same over the years, the total complement of investigators has increased dramatically so that Ph.D.'s now strongly dominate the picture. For all medical school departments there are about 55,000 faculty, of which roughly 10,000 are NIH-supported principal investigators on one or more grants, or more than 18 percent. Some departments, such as dermatology, internal medicine, and ophthalmology, are above this average, while in otolaryngology departments, about 12 percent are principal investigators on NIH-supported research

grants. Of course, these figures do not give a full accounting, because they do not capture those who are working under program project grants or in centers as other than as principal investigators.

A new report by the Institute of Medicine indicates that the Ph.D. scientist is emerging as the primary performer of biomedical research at U.S. medical schools, and credits this emergence to the rise over the past decade in the number of Ph.D. scientists on medical school faculties. PH.D. faculty in clinical departments increased by about 68 percent between 1979 and 1982, while during the same period, M.D. faculty grew by 54 percent. Furthermore, the report says, Ph.D. faculty in basic science departments increased by about 35 percent over the ten years while in contrast, the number of M.D. faculty in those departments actually declined by about 16 percent. In 1982, only 40 percent of medical school faculty who served as principal investigators on NIH grants were M.D.'s as compared to approximately 55 percent in 1972.

Clinical department Ph.D.'s were more likely than their counterparts in basic science departments to report research as a primary responsibility. Moreover, the increase in that category from 12 to 20 percent between 1972 and 1982 suggests that Ph.D.'s may have been recruited in clinical departments to compensate for the failure of the M.D. group to maintain its share of the total research effort. Although more M.D.'s in clinical departments were involved in research in 1982 than in 1972, the increase in number involved was not as rapid as for the Ph.D. segment. Consequently, M.D.'s lost ground relative to total clinical faculty research involvement.

For its part, NIH's concern over the decrease in the percentage of M.D.'s as principal investigators on NIH-supported grants, has prompted an



examination of data at hand and much discussion. The decline in the percentage of M.D. investigators working under NIH research grants reflects in part the submission of fewer grant applications by M.D.'s than by Ph.D. scientists. Another factor, of course, is the increasingly intense competition. Although during the last 10 years, NIH has shifted funds into the research grant category from contracts and other mechanisms--so that the research grant portfolio has grown from about 10,000 in 1970 to the current total of more than 18,000--competition is keen. At a time when the number of grants awarded has essentially doubled, the proportion of the meritorious applications we have been able to fund has declined to an estimated award rate of just over 30 percent. This figure reflects the fact that the applicant pool has grown faster than our resources.

The intense competition for research support has increasingly taken its toll on the undertrained investigator. The professionalization of research activity has progressively selected against the M.D. scientist who fifteen years ago had a much better prospect of success in research applications than the Ph.D. applicant. Since 1974, applicants having both the M.D. and the Ph.D. degrees have enjoyed the highest success rate, followed by those with Ph.D.'s. The M.D. scientist has been competing less well and seem to be falling farther behind each year.

Clinical research applications are more often disapproved by study section reviewers, and particularly those involving human subjects are more often assigned poorer priority scores than are applications in which no human subjects are involved. Approval rates for studies that do not involve human subjects are substantially higher than those for studies with human subjects, regardless of whether the principal investigator is an M.D. or a Ph.D.

There has been a general impression that protocols developed by physicians have suffered at study section review because the reviewers--most of them basic researchers--have a bias toward basic laboratory research studies, and fail to understand the continuum that clinical research represents. If this were the case, the problem might be solved simply by bringing in more clinical investigators to add to the review groups. But, at an NIH retreat to examine a number of peer review questions, participants reported the perception that physicians are tougher on their own clinical research colleagues than are the laboratory Ph.D. reviewers. Withal, a general feeling was expressed that, while there may be some improvements necessary to strengthen the initial review of clinical applications, the overall peer review system appears to be assuring an equitable treatment of applications for patient-oriented research.

Although much information on the review of clinical research applications is anecdotal, a study a few years ago by the Division of Research Grants provides some data.

In order to discover why applications to NIH for grants to conduct clinical research may either be disapproved or receive poor priority scores in the review process, the DRG examined 256 applications rated by 13 different study sections. For this study, clinical research was narrowly defined as research involving human subjects that included a doctor-patient relationship. The study showed that investigator qualifications and resources at their institutions played a very minor role in poor rating. Flaws in research design and conception of the hypothesis led to poor scores from reviewers. The most frequent deficiencies--faulty hypothesis

and inappropriate experimental design--were the same flaws that were cited in laboratory research proposals that were disapproved or given low scores.

The facile explanation that there is a greater inherent difficulty in working with human subjects may not be the entire answer to the lower approval rates for physician-investigators. Science has become complex, the methods intricate, and the training period so long that the physician, even after two or three years of fellowship training, remains less well trained than the Ph.D. scientist who has been training for a research career since the baccalaureate. In my own view, the trends of the past decade reflect the progressive professionalization of biomedical research, in particular clinical research. I personally hope that there will always be room for the creative amateur in clinical investigation, but recent history indicates that such a person is less and less likely to secure external support for his or her work. Success for an M.D. investigator is increasingly dependent on substantial training in the information, concepts, and methodologies of complex modern science. To be a first-rate scientist and a well-qualified physician is a demanding calling.

The importance of more and better quality training for our future scientists cannot be overemphasized. Recent analysis by NIH of four categories of postdoctorals--Ph.D.'s with NIH fellowship experience, Ph.D.'s who worked under institutional training grants, M.D. fellows and M.D.'s who trained under training grants--was very revealing. Ph.D. fellows, Ph.D. trainees, and M.D. fellows were quite successful in later attainment of NIH research grants. The percentage of "success" was 30-40 percent. We were disappointed in the track record for M.D. trainees, however. Only 20 percent of them subsequently applied for an NIH research grant, and only 10 percent actually received an award. This rather stark

difference in "success"--as defined as receiving later NIH grant support--is most likely in part due to length of training. In the post-M.D. institutional-type training programs, the median length of training is only about 12 months. Interestingly, our analysis seems to indicate that 30 months of research training is the critical minimum for achieving success in securing an NIH grant.

In a current effort to enhance research training for M.D.'s, NIH is attempting to make training grants to clinical departments more efficient. We recently advised all program directors that we are reemphasizing certain elements of the guidelines to enforce our conviction that all postdoctoral trainee physicians need longer periods of training. We would like all such trainees to commit themselves to a minimum of two years of research training, of which not less than 80 percent of the time is devoted to research. In addition, we also stress a stronger basic science component, in the hopes that M.D. trainees will become more successful competitors for research grants.

I do want to stress here that there are certainly definitions of success other than attainment of NIH research grant support, and we are examining other data as well. A preliminary examination of Veterans Administration records indicates that for every 100 NIH Ph.D. or M.D. trainees or fellows who became NIH grant recipients, an additional 19 became researchers supported by the VA. In addition, for every 100 NIH M.D. postdoctorals who became NIH grant recipients, an additional 43 became researchers supported by the VA.

We feel sure that another fraction of our trainees is meeting success through other sources of research support, for example from the private



sector and other government agencies, and we are looking into this matter further.

Given the importance of rather long and rigorous training for clinical researchers, we are also concerned that we have been failing to attract the number of qualified medical students and graduate physicians into research training. NIH has devoted considerable attention to the problem of training M.D. researchers and has introduced some major steps over the years. Many of you are already familiar with one of our most successful training programs. At the undergraduate medical student level, we have continued to give the M.D./Ph.D. program top priority in our training portfolio. We regard this 6-year program as one of our most successful in terms of building up clinical research, as it produces more than 100 graduates per year of the type of scientists who are competing most successfully for NIH research grant support. In addition, more than 1,000 medical students in standard curricula this year availed themselves of off-quarter training opportunities supported by NIH. The NIH also offers summer research experience at the NIH campus. We are about to enter the second year of the NIH-Howard Hughes Medical Institute program which brings about 38 medical students to NIH annually to work with top scientists for periods of 9 months to a year.

The physician who has completed four years of medical school and several years of clinical training is, by and large, only modestly, if at all, prepared with research skills. Even when this M.D. has participated in research projects, the experience does not substitute for a planned program to develop research expertise. For this reason we offer several career development programs that are deeper and longer than the fellowship/traineeship approaches. The Clinical Investigator Award has been

particularly successful in attracting physicians for three to five years of supervised research development. Another award in the career development series is the Physician/Scientist award, designed to provide five years of phased supervised research development. These are made primarily as individual awards, based in departments with established records in producing physician-scientists.

NIH's commitment to the continuance of clinical research goes well beyond regular research grant support for clinical investigators and training of physician-scientists. As I mentioned at the start of my talk, the NIH mission is broad and encompasses activities concerned with technology transfer activities such as clinical trials and procedure evaluations. Without a doubt, countless physician investigators are supported through these NIH-funded programs, and we believe they have met with success in diffusing new concepts and techniques, and technologies into the health care system. If we define a clinical trial as one involving 10 or more patients, then NIH supported 3,000 such studies in 1985.

The NIH clinical center itself, with its Ambulatory Care Research Facility added in 1981, is a setting where laboratory and clinical research, research training, and transfer activities--such as clinical trials--go on simultaneously. Similar are the NIH-supported General Clinical Research Centers (GCRCs), 72 of them located around the country, providing environments for 80 percent of the patient-oriented research for the grant programs of the NIH categorical institutes. More than 3,500 projects are conducted at the GCRCs each year by a small army of investigators, many of whom receive support from NIH research grants,

training grants, program project grants, contracts, or career development awards.

A rather different kind of transfer activity is accomplished by NIH consensus development conferences whereby data on controversial medical topics or questioned procedures are examined in public session by a broadly based panel of experts. The findings and recommendations of the panels are subsequently made available to the public and to practicing physicians. This is an example of NIH activity that goes somewhat beyond the traditional NIH mission of research support.

Many of you are already familiar with the broad mandate of the National Cancer Institute (NCI) in searching for more effective methods of treating cancer and making new approaches available as widely and rapidly as possible. The NCI gives core support for administrative costs and shared resources to 56 cancer centers scattered across the country. Sixteen of these are specialized centers devoted solely to laboratory research. The rest, including the 20 comprehensive cancer centers, have both clinical and basic research programs. Community Clinical Oncology Programs are a unique way of providing support to community physicians and hospitals through the network of cancer centers. In this relatively new program, research protocols have become available to thousands of patients without their having to travel to major medical centers. By increasing the number of patients in treatment studies, the program is also expected to reduce the time needed to find answers to important questions about new therapies. This community based program takes advantage of NCI's training programs of the 1970s.

In addition, more than 4,000 cancer specialists and researchers at hundreds of institutions in the U.S. and abroad are members of Clinical

Cooperative Groups supported in part by the NCI. Each Cooperative Program studies one or more kinds of cancer and assists in the clinical evaluation of new anticancer drugs and other investigational approaches to treatment. Much of the improvement in 5-year survival statistics can be attributed to the widespread participation of cancer patients in clinical research protocols carried out by the Cooperative Groups. In your own specialty, clinical trials have demonstrated the effectiveness of neoadjuvant chemotherapy in patients with advanced head and neck cancer. These cooperative trials have accomplished a 90 percent 5-year survival rate for patients who obtained complete remission with chemotherapy and who were subsequently treated with surgery or radiotherapy. Without neoadjuvant chemotherapy, the 5-year survival rate was only 20-30 percent. In the new study, one third of the patients with advanced cancer had a complete response to their treatment.

Given the National Cancer Institute network of programs, it is not surprising that fully 15 percent of cancer patients in this country are treated under protocols in these NCI-supported activities. It is also noteworthy that these programs could not exist today had not the NCI--a decade or more ago--seen the need to train oncologists for the increasingly demanding practice of treating cancer patients with newer, more sophisticated approaches.

These NCI programs knit together closely the three elements important to NIH's mission--first, building a knowledge base through research; second, nurturing a cadre of scientists and physician-scientists trained in modern science; and third, transmitting into the medical setting the fruits of research.



I hope that this brief review of NIH programs in clinical research and training serve to underscore the abiding commitment that we have to patient-oriented research as an indispensable element of our activities.

## A LOOK INTO THE FUTURE - NEW ADVANCES IN HEALTH CARE\*

by

James B. Wyngaarden\*\*

I am very honored and happy to be here this evening for the 37th annual McLeod Seminar. In my talk, I would like to mention some recent advances in biomedical research that are beginning to have an impact in the health care setting--in particular, advances that can be seen as a part of the so-called "new era of biotechnology". Further, I would like to make some observations about biomedical research as a factor in the cost of health care provision.

Just a little more than a year ago--April 19, 1985, to be exact--officials of the National Institutes of Health and the Food and Drug Administration, five pediatric endocrinologists, a neurologist, and representatives of several pharmaceutical companies met in a small conference room at the NIH in Bethesda, Maryland. They were gathered to make an important decision with implications for the approximately 3,500 patients in the United States being treated with human growth hormone, their families, and the 150 physicians who had been treating the hormone-deficient children. Before the end of the day, the group recommended

---

\*Keynote address given at the 37th Annual McLeod Seminar at Florence, South Carolina, April 8, 1986.

\*\*Director, National Institutes of Health.

to the Assistant Secretary for Health that he suspend the distribution of human growth hormone through a program supported by the NIH. The recommendation was accepted immediately and plans were made to inform swiftly all those concerned with the action.

The decision was prompted by a report to NIH just one and one-half months earlier that a young man who had been treated with human growth hormone supplied through the NIH program had died of the rare, neurological disorder, Creutzfeldt-Jacob disease, five years after this hgh therapy had ceased. This was followed by reports in early April of the death of two more hgh-treated patients, apparently also of the slow virus disease.

Although it appeared likely that the three patients had received hormone contaminated with the Creutzfeldt-Jacob virus prior to 1977--when the purification procedure was improved-- the group recommended that all distribution of the product be halted as a safety precaution. The decision to stop the supply, however, was not an easy one. Links between the use of the hormone and the fatal viral disease were circumstantial and could not be confirmed until animal transmission studies could be completed--a process that could take 2 years!. Furthermore, some children, those with life-threatening hypoglycemia, needed the hormone immediately. And there was, of course, concern for the children who had been responding well to the hormone and would cease to grow if deprived of the treatment.

Fortuitously, timing was right. Scientists at the University of California and Genentech--one of the earliest biotechnology firms--had for some time been working on a genetically engineered version of hgh and as early as 1979 had met with a measure of success. Genentech had been producing its synthetic product--Protropin--in significant quantities since 1980 and had been running clinical trials since 1981. Safety and efficacy trials had

already progressed to the point where the Food and Drug Administration was able to approve Genentech's recombinant hgh in October 1985, just six months after the natural product was pulled from the marketplace.

In the period between April and October, the FDA also gave the genetically engineered product Investigational New Drug status so that doctors could prescribe it immediately to the 150 or so children who would die without it.

This incident illustrates several points, I believe--first, the need for government, private industry, and practicing physicians to work together in managing such crises and second, the need to push forward the frontiers of medicine through research. It is not the nature of the biomedical research and development enterprise to become complaisant. In fact, a number of companies are currently working on a second generation of recombinant hgh, one more like the natural product, with the promise of helping even more patients--perhaps as many as 14,000-- those who could not be helped by the natural hormone because of its critical shortage.

Of course, not all new products born of recombinant DNA research will enter the marketplace with such drama.

Genetically engineered hgh was preceeded into the marketplace by recombinant insulin in 1982. Today, fifty percent of newly diagnosed diabetics who require insulin are put on this synthetic type. Other genetically engineered products in research and development phases or under evaluation by FDA are alpha, beta, and gamma interferons--primarily for use against various cancers and viral infections--and tumor necrosis factor and epidermal growth factor for cancer treatment. And of course, the interleukin-2--used by Dr. Stephen Rosenberg in his recently reported cancer trials--is of recombinant origin.



Two recombinant DNA diagnostic probes were approved in Fall of 1985: one for Legionella and one for herpes simplex. A third major application of recombinant technology is in vaccine development: NIH clinical trials of recombinant hepatitis B vaccine have already shown it to be safe and even more immunogenic than the currently approved vaccine. Other important recombinant vaccines are on the horizon--for herpes I and II, for falciparum malaria, and for cholera.

Within the next year, it is likely that a proposal to perform gene therapy in humans will be submitted through local review boards and through the National Institutes of Health by one of the eight to ten laboratories now pursuing molecular genetic approaches to correction of selected inborn errors of metabolism. The likely candidate diseases for which gene therapy will initially be attempted are severe combined immunodeficiency (SCID) due to adenosine deaminase deficiency and the Lesch-Nyhan syndrome. While gene therapy, to the public, may sound revolutionary as an approach to human genetic disease, the techniques likely to be used in the near future closely resemble those of conventional medical practice--essentially autologous bone marrow transplantation with an extra step, addition of a properly functioning gene to as many target cells as possible.

Monoclonal antibodies were discovered only 10 years ago by Kohler and Milstein, of Cambridge, an achievement that earned them the Nobel Prize for Medicine in 1984. In the short time since that discovery, these protein molecules with their amazing specificity for chemical constituents of living cells, have become standard tools in biological research. Their utility has been extended well beyond basic research and is being extensively applied by the U.S. biotechnology industry. The impact of monoclonal antibody technology is especially strong in the area of in vitro diagnostic products, for example:

those to detect pregnancy and ovulation, to diagnose infectious diseases such as strep throat and hepatitis B, to identify pregnant women with the potentially dangerous Rh antigen, and to identify biochemical tissue markers for organ transplant procedures and detect tumor markers in blood and other specimens from cancer patients. The FDA has already approved more than 150 diagnostic kits that use monoclonal antibodies, most of which are expected to produce results much faster than microbiology-based tests.

Other monoclonals under development are aimed at diagnosis of disease in vivo. One of the most sophisticated of these products centers on tumor imaging processes to allow physicians to establish the location and extent of a tumor. It is based on radioactive isotope labeling of tumor-specific antibodies, with recording by gamma camera, a standard piece of equipment in most hospital laboratories. Also under development is a technique that combines use of monoclonal antibodies with NMR imaging. Monoclonal antibodies are also being developed for use in cardiac imaging, where an antibody specific for myosin can help differentiate between recoverable heart tissue and that irrevocably damaged by heart attack.

Using monoclonals for direct treatment lies further in the future. Some day cancer patients may be administered unmodified monoclonal antibodies or monoclonal antibodies bearing toxin molecules. Such molecular conjugates would be designed so that the monoclonal portion specifically recognizes a malignant cell and the toxin portion, once inside the cell, destroys it. But the theory has practical difficulties--if there is central nervous system involvement, antibody use would be inappropriate as they cannot cross the blood/brain barrier well. Moreover, finding tumor-specific antigens is difficult, and avoiding immune reactions to foreign antibodies--especially when repeated administrations are needed--might be difficult.

Similar application of monoclonal antibodies in heart disease already seems promising. Experiments in animals have shown that streptokinase--or another lytic agent--plus a monoclonal antibody specific to cross-linked fibrin, can dissolve thrombi in the femoral arteries with fewer systemic effects than are found with other therapies. Injected intravenously, the drug is guided by the antibody to the exact area containing the clot, and the streptokinase works as always, by activating the conversion of plasminogen to plasmin. Following human studies, the system may be useful in myocardial infarction patients, and in those with stroke, pulmonary embolism, and deep-vein thrombosis.

Clearly, recombinant DNA and monoclonal antibody techniques are exceedingly powerful tools for research. The initial optimism for their application in pharmaceuticals, I believe, has already proven to be warranted. But what can be overlooked in all the excitement about the coming applications of biotechnology is the solid foundation of basic research in the life sciences that undergirds these current efforts. Research done in the universities and medical schools around the country, most of it supported by the NIH, has contributed enormously. A recent article in the Washington Post about biotechnology stated, "Although universities, venture capitalists, scientists and entrepreneurs all have played key roles in the industry's growth, the critical factor has been 30 years of growing support for basic biomedical research." Scientists supported by NIH had no idea that their research would eventually contribute to the development of gene splicing, a crucial advance that would lead to recombinant DNA technology. Arthur Kornberg of Stanford, who won a Nobel Prize in 1959, put it in personal terms in a recent essay: "In these explorations (on basic aspects of DNA and RNA) I neither anticipated nor promised their industrial application. Nor did any of

my colleagues with comparable federally-funded projects." "In short," he said, "the genetic engineering industry spread out before us sprang entirely from the pursuit of irrelevant research in universities made possible by the investment of many hundreds of millions of dollars by federal agencies over more than two decades."

As is obvious from my foregoing remarks, biomedical research continues to fuel technology, which in turn seems to be offering up more and more advances with direct application in the health care setting, at what seems to be an ever increasing pace. This phenomenon raises concerns about the possible impact of biomedical research upon the cost of health care. The concern seems realistic when you consider the following: National outlays for health, which were \$355 billion in 1983, could jump by as much as \$100 billion a year in 1983 dollars by the end of the century and reach 14 percent of the GNP solely from the added costs of new technology!\*

Many highly technical procedures for diagnosis and treatment now coming into frequent use are truly miracles of modern medicine, but often they are very expensive and constitute a powerful force driving upward the cost of medical care. In the context of these developments, we encounter a paradox; namely, that a substantial number of medicine's discoveries in recent years have increased rather than decreased the cost of medical care. Experts in health care and research are warning that costly medical procedures--coronary bypass surgery, sophisticated new imaging systems, heart and liver transplants--could result in vast additional health outlays in the next decade.

---

\* According to the American Enterprise Institute



In this regard, we are left with two challenges: First, to continue research that will bring us beyond the highly expensive halfway point in treatment of disease--as has been the mission of the NIH and institutions such as this for at least a century. And second, to develop data more useful in convincing those who make decisions about spending for biomedical research, that our work also contributes to cost savings in health care.

In an attempt to gather some data to counter the general view that research advances tend to drive up the cost of health care, I recently asked the various NIH components to provide some recent examples of advances in biomedical research that have reduced health care costs. Although we must consider these as estimates, based by necessity on assumptions, you may find a few of them interesting:

o Research in San Francisco supported by the National Heart, Lung, and Blood Institute (NHLBI) conducted on sheep implicated prostaglandins in maintaining patency of the ductus arteriosus. This led to treatment of newborns with the patent ductus syndrome with the prostaglandin synthetase inhibitor, indomethacin, for medical closure of the ductus. This treatment is successful in about 85% of cases. The NHLBI has estimated that use of indomethacin in patent ductus arteriosus (PDA)--as a substitute for surgical treatment--saves approximately \$180 million annually. We have estimated that approximately 20,000 premature infants have significant PDA necessitating treatment and that each surgical procedure would cost \$3,000, with an additional \$6,000 per patient for 6 days in an ICU. On the other hand, we estimate that a full course of medication costs only \$40 per patient.

Interestingly, the research leading up to this net savings, including basic research and clinical trials, cost only about \$10 million.

- o Based on results of their Coronary Artery Surgery Study, the NHLBI estimates that approximately 25,000 coronary bypasses could have been deferred in 1983 in favor of management through medical care and drugs. If the indications from the study were widely applied, there would be the potential for reducing health care costs for these 25,000 patients from nearly \$506 million to a little more than \$8 million, for an annual net savings of nearly \$500 million. This study cost NIH \$26.5 million over 10 years.

- o A more recently reported study is the clinical trial supported by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) indicating that a widely used neurosurgical procedure to prevent stroke or stroke death is no more effective than aspirin and standard hypertension control. If the conclusions of this study were followed widely, it is believed that thousands of extracranial/intracranial (EC/IC) bypasses now performed annually in the U.S., at an estimated cost of \$15,000 per operation, could be avoided with savings of at least \$30 million.

- o Antenatal steroid therapy in high risk pregnancies has proved to be of benefit in the prevention of neonatal respiratory distress syndrome. The NHLBI estimates net annual savings of about \$295 million from this relatively new therapy based on 50,000 cases of neonatal RDS per year. The clinical trial to study the efficacy of the steroid treatment cost approximately \$5.5 million.

- o Aside from major clinical trials, savings from the gradual accumulation of knowledge applied by degrees, can lead to tremendous savings difficult to quantitate. Advances in diagnostic imaging techniques have had an enormous impact both in reduction of health care costs and increased safety and

comfort. Today, brain tumors can effectively be diagnosed and followed for response to treatment with a simple 45-minute outpatient computer tomography scan. Before this development, diagnostic procedures were likely to include costs for EEGs, nuclear medicine scans, arteriograms, or pneumoencephalograms. Similarly, pretreatment staging of a child with Wilm's tumor might have included intravenous pyelogram, inferior venacavogram, or retrograde pyelogram. Not only did these procedures give a relatively poor characterization of the tumor, but they were both expensive and uncomfortable, making it difficult to repeat studies and follow disease response.

- o Therapy of soft tissue sarcomas with wide local excision and radiation, rather than by amputation and subsequent prostheses, reduces the cost of treatment per person from \$50-80,000 to \$8,500. NCI intramural clinician-scientists along with others have shown this new mode of treatment to be efficacious in an increasing number of selected patients. However, while this is a saving for individual patients, it would not have a great impact in the aggregate, as this type of cancer is relatively rare.

- o The National Eye Institute developed fairly solid figures relating to laser treatment for several blinding conditions. For three such disorders--angle-closure glaucoma, aging-related maculopathy, and diabetic retinopathy--taken together, laser treatment has lowered annual costs from about \$260 million to about \$106 million. Because no effective therapy was available for two of these conditions prior to development of laser treatment, the annual costs were based on estimates of the annual cost to society for support of blind individuals. The research leading up to the laser therapies--excluding basic research--cost only about \$13 million. This was primarily the cost of running the clinical trials to prove efficacy.

o Another noteworthy example is percutaneous transluminal coronary angioplasty. It was estimated by the NHLBI that 17,000 coronary artery bypass graft procedures for single vessel disease could be replaced by angioplasty. At a cost of \$20,000 per patient for the surgery as compared with \$6,800 for each angioplasty, the annual savings would be more than \$156 million, even when you consider that about 20% of the patients initially having angioplasty would subsequently require a bypass graft.

o Advances relating to child health have enormous potential for saving in health care costs. The National Institute of Child Health and Human Development (NICHD) estimates that owing to our current ability to assess fetal maturity and thus prevent prematurity associated with cesarean delivery, we are annually saving approximately \$325 million, with the problem almost entirely eliminated. Development of a screening test for hypothyroidism--at a cost of about \$1 million for research--has reduced annual costs for treatment by a net of more than \$10 million.

o The development of specific criteria for tonsillectomy to relieve recurrent throat infections has led to a large decrease in unnecessary surgical interventions. It is estimated that development of the criteria, based on NICHD-supported studies, saved about \$818 million in 1985. These examples alone total a savings of \$2.5 billion a year--about one-half our total budget--and I've only selected a few illustrations.

But in spite of such examples, the list of human diseases for which there are as yet no definitive measures for prevention or cure is still formidable. Fresh insights into the nature of these diseases are needed. And these insights can come only from continued basic research. Some of our critics have claimed that there is an abundance of scientific knowledge locked in the



laboratory merely awaiting a new emphasis on human application. I do not believe this to be true. Most of the critical bits of knowledge about these diseases have yet to be discovered.

In spite of the high cost of contemporary medicine, I remain bullishly optimistic about the future of medical care, and believe that if we persist, one by one these expensive technologies that are now life saving will be rendered as obsolete as the iron lung and replaced by yet more effective, simpler, inexpensive measures. But we must continue to search.

In closing, permit me to use the familiar quotation from Lewis Thomas, in which he added "halfway technology" to our lexicon and stated a truth about which we need to be reminded periodically. Here are his words: "I say that we must continue doing biomedical research on about the same scale and scope as in the past 20 years with expansion and growth of the enterprise being dependent on where new leads seem to be taking us. It is an expensive undertaking . . . but it is still nothing like as expensive as trying to live with the halfway technologies we are obliged to depend on in medicine today; if we are to try to stay with these for the rest of the century, the cost will go through the ionosphere."

# Biomedical Research, NIH and the Budget\*

by

James B. Wyngaarden, M.D.\*\*

Next year we will celebrate the 100th birthday of the National Institutes of Health (NIH). Within the coming months, we will be announcing a variety of events and activities to mark the centennial. The theme will be "A Century of Science for Health." Today I will mention some of that history from 1945 to the present as it relates to the current outlook for funding biomedical research.

The 40-year period since the end of World War II is the era of the modern NIH--the Agency as we know it today. The war years brought dramatic changes to the small Federal laboratory known as the National Institute of Health. Almost all of its research activities until that time had been in-house, but under the stress of war, universities, medical schools, hospitals and other laboratories were drafted into a partnership with the Federal Government to meet the pressing needs for medical research. The NIH, that prior to 1940 had been almost exclusively an intramural operation, began by the late 1940's to rely more and more heavily upon its extramural programs in carrying out its mandate. In recent years, the commitment of funds to the extramural components has represented about 88 percent of the Agency's total budget.

## History of the Budget

Addition of the extramural dimension to the NIH was accompanied by increases in budget--increases that for a part of the time from 1945 to the present have been spectacular. (Slides 1a, 1b, 1c)

Two major phases of our growth in the past 40 years are apparent from this set of slides. In terms of purchasing power in constant dollars, the total budget of NIH grew from 1945 to 1968 at an astounding average rate of 24 percent per year. The growth per year since 1968, taking inflation into account, has been much less--about 2 percent per year.

By the mid-1960's, when the steep climb in the NIH budget began to taper off, dedicated proponents of biomedical research took the offensive first under the banner of initiatives against heart disease, cancer and stroke and, a few years later, of "a war against cancer." For a time, the Democratic

---

\*Address given at the AAAS Pacific Division Conference,  
Palo Alto, California, April 10, 1986

\*\*Director, National Institutes of Health, Bethesda, Maryland

Congress and the Republican Administration attempted to outbid each other in terms of appropriation and organizational innovations to hasten the conquest of cancer. Subsequently, proponents of research on heart disease followed suit.

Between 1971 and 1973, the budget of the National Cancer Institute more than doubled in current dollars. It tripled by 1975. The National Heart, Lung, and Blood Institute also experienced a period of rapid growth, increasing by 35 percent between 1971 and 1973 and doubling by 1977. The budgets of both these institutes grew faster than the total NIH budget during the early seventies and consequently most other components had reductions in purchasing power for 5-7 years. Thus, without much growth for NIH as a whole there was a remarkable revision of national priorities toward cancer, heart disease and to a lesser extent stroke. By the later seventies, however, the growth differentials between institutes had largely evened out.

#### Growth of the Research Project Grant Budget

An examination of the NIH budget for the period beginning in 1972 and continuing to the present also reveals adjustments in the use of the various mechanisms for carrying out research. The salient feature of these adjustments was the marked shift in the allocation of funds to favor the support of research project grants. In the period from 1972 to 1984, the budget for research project grants increased from 44 to 66 percent of the extramural budget, and that for all research grants from 62 to 84 percent. There was a concomitant reduction in budget for contracts and training. The total number of such project grants being supported during 1972 was 10,290, and by 1985 the number had grown to 18,219. Throughout this time, the average award per project remained virtually unchanged in constant dollars. However, indirect costs took an increasing share of the research award, rising from 21 percent in 1972 to over 31 percent in 1985. Consequently, the real dollars available per project for direct costs were reduced. (Slides 2, 3, 4)

#### Growth of the Applicant Pool and the Stabilization Initiative

Another pressure has developed, not directly the result of the budget crunch, but an effect of the progress of science. The number of excellent applications for grants increased at a much more rapid rate than our ability to fund them. The number of competing applications for project grants reviewed in 1985 was 18,674, more than double the number reviewed in 1972. (Slide 5)

In the past decade, we have become increasingly concerned about maintaining a relatively stable and predictable level of new and competing renewal project grants. The number of competing awards has fluctuated greatly since 1972, ranging from a total of 2,592 in FY 73 to a high of 6,246 in 1985. Such fluctuations not only create financial problems for grantee institutions but adversely influence the career decisions of graduate students as well as young scientists. (Slide 6)

We have recognized that to assure future health gains, the current national research capability must be sustained and enhanced. As applied to research project grants, a major goal has been to minimize the year-to-year fluctuations in the number of competing grants in 1979. The goal of funding



at least 5,000 new and competing renewal grants atop a base of moral commitments of 11,000 continuation grants was defined as a major feature of the "stabilization" policy.

With the presentation of the FY 1987 budget, however, the Administration proposed a new research grant stabilization policy. Under this new policy the total number of NIH research project grants would be stabilized at 18,000. The new definition of the level of stabilization is very near the all-time high in number of grants that was reached in 1985 when 18,249 awards were in effect. In a moment I will touch on some of the implications of the new stabilization level as they relate to the FY 1987 budget. While the stabilization strategy is useful in defining a basic level of needed support, it would be incorrect to contend that the maintenance of a number of grants in itself assures stability for the research programs of the NIH. In recent years the priority of research grants has resulted in less funding of centers, training and clinical trials.

#### Increased Competition and Some of Its Effects

However, in spite of the progressive annual shift of funds into research project grants, the number of applications has grown even faster than resources. In 1975 we were able to fund about 65 percent of grants eligible for award, but in 1984 and 1985 the award rate was only about 37 percent. (Slide 7) As would be predicted, the paylines are progressively lower.

(Slide 8) Another result of fiscal restraints plus competition, is that with increasing frequency, grant proposals are being resubmitted after unsuccessful competitive review. In 1965, 6 percent of applications reviewed were resubmissions--in 1975, it was 15 percent, and by 1985, we estimate the proportion of resubmissions to be 25 percent of all applications.

#### The Awards Process Revisited

Although fiscal constraints are responsible for many of the difficulties I have been discussing, certain attributes of the current extramural award system may be more burdensome than necessary for the investigator, the university, and the NIH peer review system.

In order to increase productivity of the resources we have instituted several changes of the review and award process. In our judgement one of the factors that is contributing needlessly to the workload of both the grant applicant and the NIH peer review system is the excessive complexity and sheer bulk of the research grant application. The great majority of applicants are aware that the competition is tougher than ever. The word gets around that study sections often look for minor flaws or omissions in applications under review and that small factors shift priority scores. Based on such wisdom, the applicant tends to overdocument, to go to extremes to shore up whatever he or she perceives to be possible weak spots. As a result, the workload for both applicant and study section is greatly increased. To counter the trends we will shortly be proposing page limitations on grant applications. This should reduce reviewing time of study section members as well as preparation time for the applicant.



When the award rate falls, the percentage of first-time applicants receiving awards also falls. We believe it is essential to the vitality of the scientific enterprise and to the morale of the field that young scientists be encouraged. We have recently announced a new program called FIRST awards (First Independent Research Since Training)--a modification of the R-23's which raises the award from 3 to 5 years and the total to \$350,000 of direct costs for the 5 years. This should obviate the difficulty of too early reapplication for investigators whose initial 18 months runs into difficulties and also encourages more creative, less defensive, research.

Finally, we have also expanded the number and type of longer term support for outstanding mid-career scientists, through a new program called MERIT awards (Method of Extending Research in Time). This program will involve facilitated extensions of 5 year awards for an additional 3-5 years on the basis of a detailed progress report rather than a formal reapplication--although the extension will count as a competing renewal in our tally in order to remain within our ceilings of numbers of active awards. We believe that a greater number of longer grants to both first-time and established investigators represent an efficient and prudent investment of Federal funds. However, the budgetary implications in the 4th and 5th years and beyond are substantial and, in the absence of major funding increases, could reduce the number of new and competing renewal grants we would be able to make in future years.

#### The Infrastructure

Over the past decade, increasing concerns have been widely expressed concerning obsolescence of research instrumentation and facilities in the Nation's research universities.

A study of instrumentation jointly funded by the National Science Foundation and the NIH was completed last year. The study documents the trends in the amount, condition, and cost of existing research instrumentation in the Nation's principal research universities, and the nature and extent of the need for upgrading research instrumentation. The report, not surprisingly, showed a national need for newer equipment in many laboratories, particularly public institutions. The outstanding need seems to center on relatively low cost instruments in the \$10-75,000 range, perhaps reflecting some degree of success in warding off critical needs for large instruments through the ongoing NIH programs for sharing such instruments.

#### The NIH Budget for 1986 and for 1987

At our recent hearings on the FY 1987 budget for the NIH before the House and Senate Appropriations Subcommittees, I told the Members that we understand the need for strong measures to reduce the Federal deficit, and that the budget we presented was an example of the kind of restraint the times require of the non-exempt components of the Government. I told the Committees that we will do our best to maintain the stability of the Nation's biomedical research enterprise and the momentum of its recent progress, but that our ability to do so would require maximum flexibility so that we can take maximum use of our resources to take advantage of scientific opportunities. It was in this context that I made our presentation.

Before discussing the FY 1987 proposal, however, it is necessary to take into account certain adjustments in the FY 1986 budget. The original 1986 appropriation to NIH was about \$5.5 billion. This amount has been reduced by \$236.2 million as required by the Balanced Budget and Emergency Deficit Control Act, better known as Gramm-Rudman. The 4.3 percent decrease has been applied uniformly against the appropriation of each Institute and Division, as well as against each research mechanism at the NIH aggregate level, and each identified program, project or activity. To apply such a reduction in such a way is not a simple problem, in that it involves a three dimensional matrix.

Further, certain special problems arise because of the composition of the budget of certain of the entities to which the 4.3 percent reduction was applied. For example, the largest element by far of the intramural program costs is in salaries. It is not possible without total disruption to make a sudden reduction in personnel. Consequently, a 4.3 percent reduction in such programs quickly translates to a 15 to 20 percent reduction in necessary supplies and purchases for intramural programs. The problems in the extramural world are similar. Another complication arises from the language of the appropriation under which we are operating that requires us to make 6,100 new and competing grants. Because we do not plan to apply the Gramm-Rudman reduction to previously awarded grants, it will be necessary for us to reduce the amounts of new and competing grants by 7 to 8 percent on the average, I suspect.

A rescission of \$77 million is also proposed, in addition to the Gramm-Rudman reduction. Most of the rescission is designed to apply to research project grants as part of the new stabilization policy, and if it is approved would reduce the number of new and competing grants for the current year to 5,500, and they would be cut by an average of 6 to 7 percent each.

These reductions, together with a change in the method of funding AIDS research, bring the FY 1986 budget to a bit less than \$5.1 billion. The President's request for FY 1987 is just over \$4.9 billion. This is a 2.6 percent decrease from the revised '86 figure, but about an 8 percent decrease from the original 1986 appropriation.

The proposed 1987 budget provides for the new stabilization level of 18,000 grants. Allowing for continuing grants, this level would permit 5,130 new and competing grants, but it would be necessary to reduce their amounts by an average of 12 to 15 percent from the study section recommended level. Such reductions would be made on an individual basis, taking heavily into account the adjudged merit of the proposals. Application of the reductions would vary from institute to institute. But in this context, it will be difficult to make any headway in repairing the instrument deficit, for example.

Second only to our priority for investigator-initiated research projects is the importance we attribute to research training. In the FY 1987 budget, request is made for \$198.2 million for training for the support of about 9,250 predoctoral and postdoctoral trainees--a reduction of 700 from the proposed 1986 level of 9,950 and of 1,374 from the 1985 level.

Other extramural research mechanisms will be maintained at approximately their FY 1986 funding levels. Two exceptions are the Biomedical Research Support Grant (BRSG) Program and the Extramural Facilities Construction

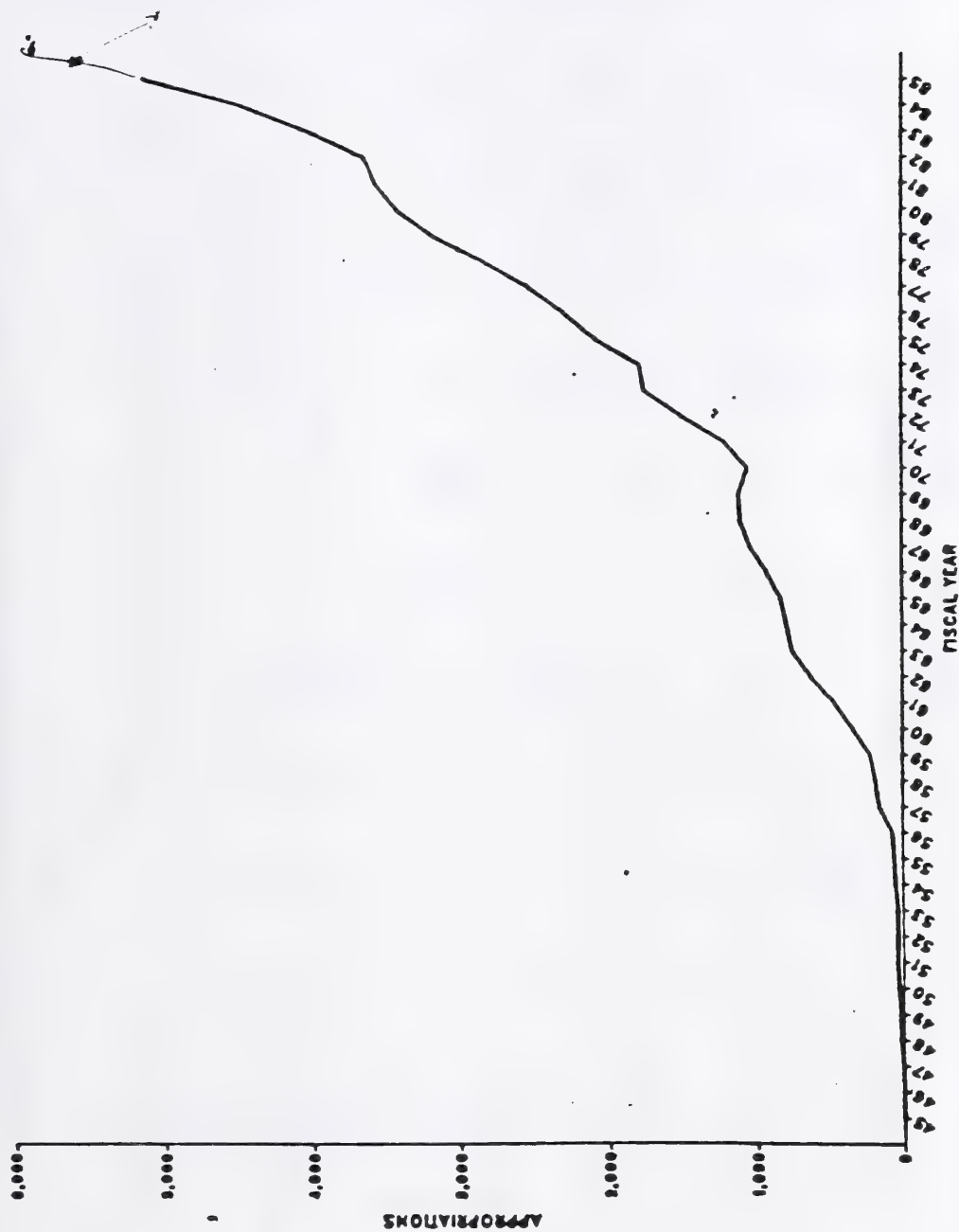
Program, both of which will be eliminated in FY 1987. Because of the continued emphasis on investigator-initiated project grants as the most appropriate form of support, and in the face of growing concern over the total budget, the EFG must rank as a lower priority when compared with other NIH programs. The Extramural Facilities Construction Program is also proposed for elimination due to budgetary constraints and the relatively lower priority of this program.

A new method of reimbursing grantees for the indirect cost portion of NIH grant awards is assumed with the 1987 NIH budget. This proposal reflects the concerns commonly expressed in the Congress and the Administration over the escalating costs of research. The new policy would set a national maximum limit for academic grantees on the reimbursement rate for the administrative overhead costs that constitute approximately one-half of all cost reimbursements to grantees. Beginning in FY 1987 the new policy would cap reimbursement for such administration at 20 percent of the grant's direct costs as compared with the current average of 26 percent for this cost element. Implementation of the new policy is expected to reduce indirect costs by an estimated \$85 million.

I have mentioned most of the significant features of the FY 1987 budget and would be happy to respond to any questions you may wish to ask.



# Total NIH Appropriations in Current Dollars, FY 1945-85 Excluding Programs Transferred Out (Dollars in Millions)

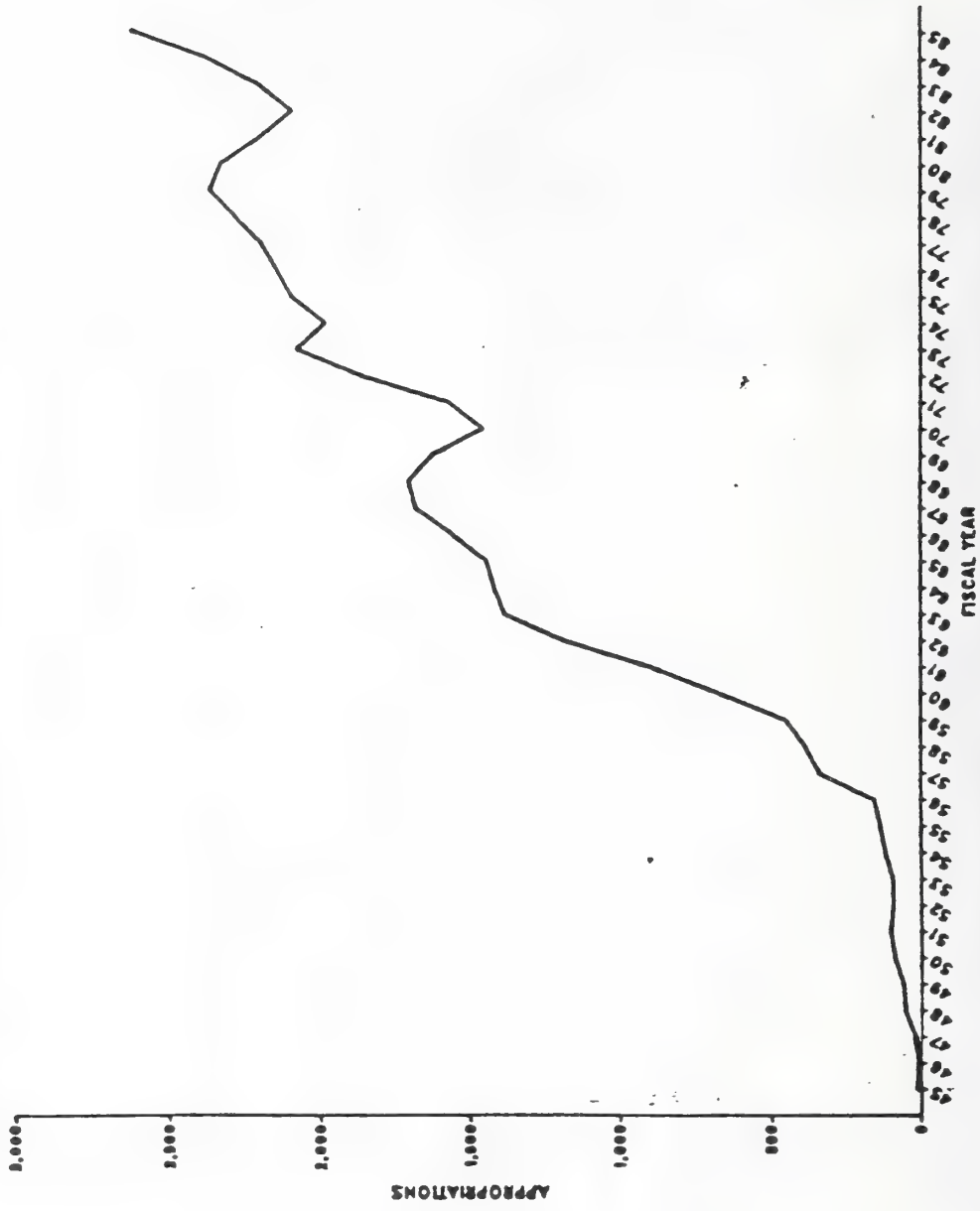


NOTES: TO excluded. 1985 data preliminary.

PAB/DPA/OPPE/OD, April 1985



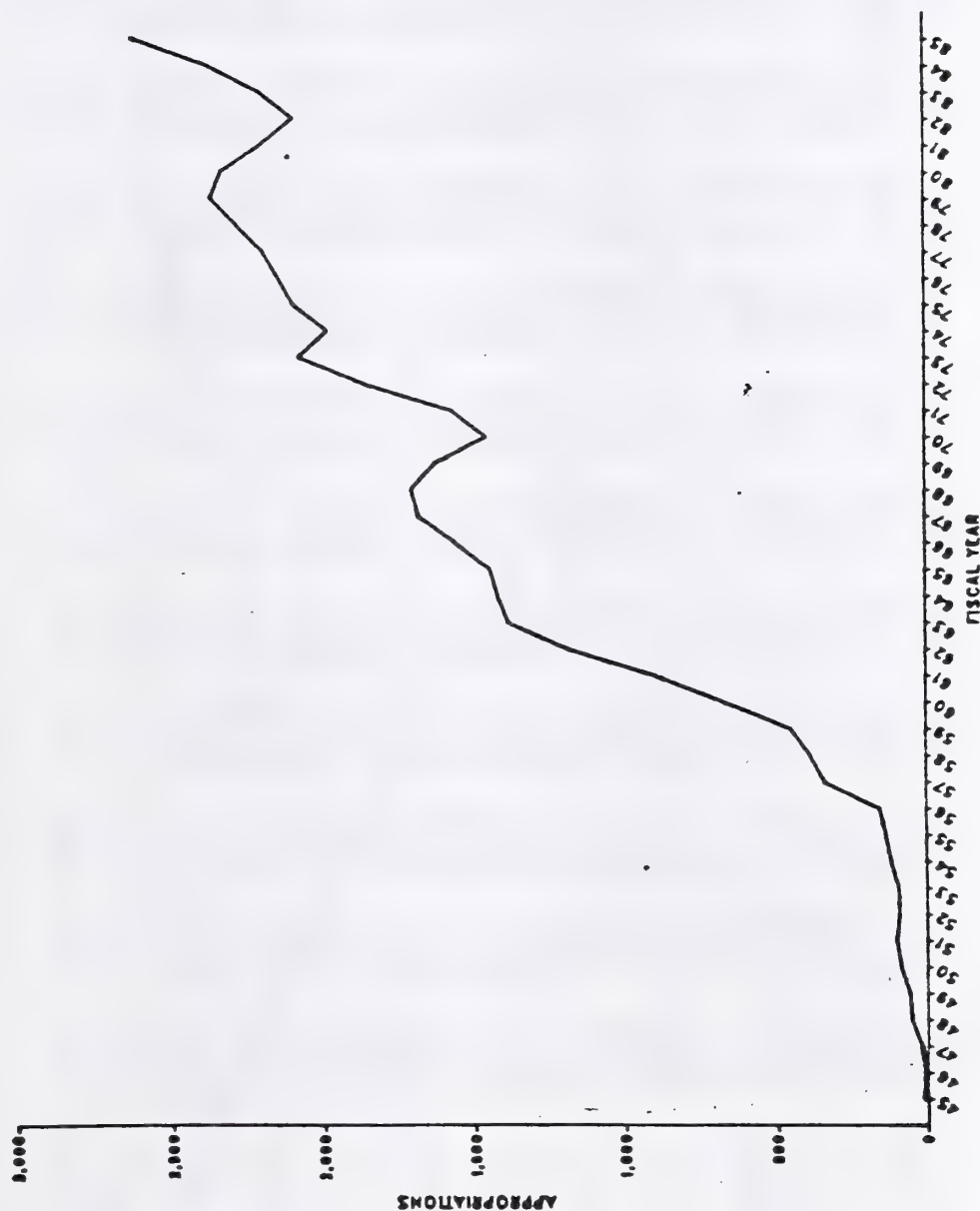
Total NIH Appropriations in Constant (1975) Dollars, FY 1945-85  
Excluding Programs Transferred Out  
(Dollars in Millions)



NOTES: Constant dollar conversion uses BRDPI. TQ excluded. 1985 data preliminary.

PAB/DPA/OPPE/OD, April 1985

# Total NIH Appropriations in Constant (1975) Dollars, FY 1945-85 Excluding Programs Transferred Out (Dollars in Millions)

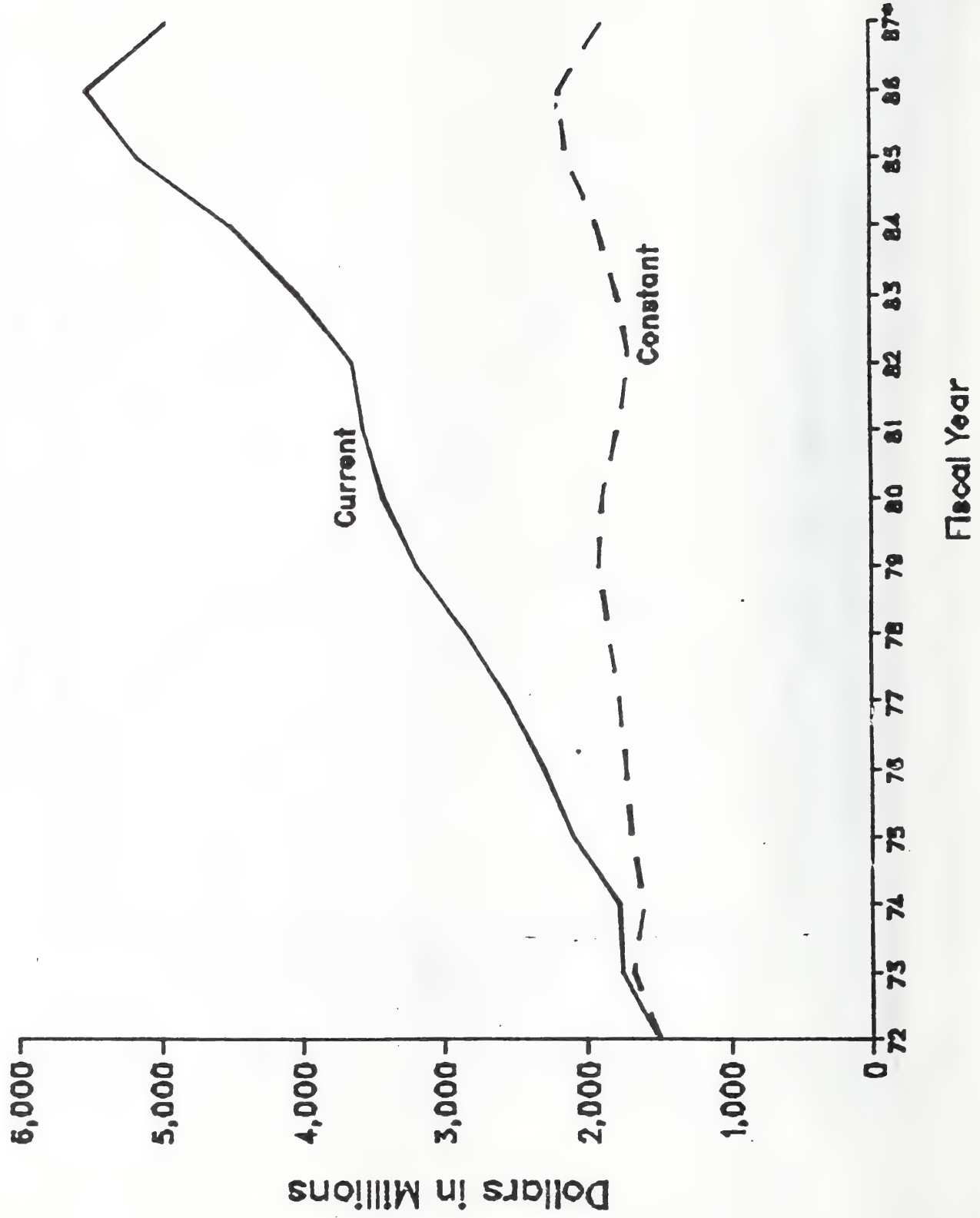


PAB/DPA/OPPE/OD, April 1985

NOTES: Constant dollar conversion uses BRDPI. TQ excluded. 1985 data preliminary.

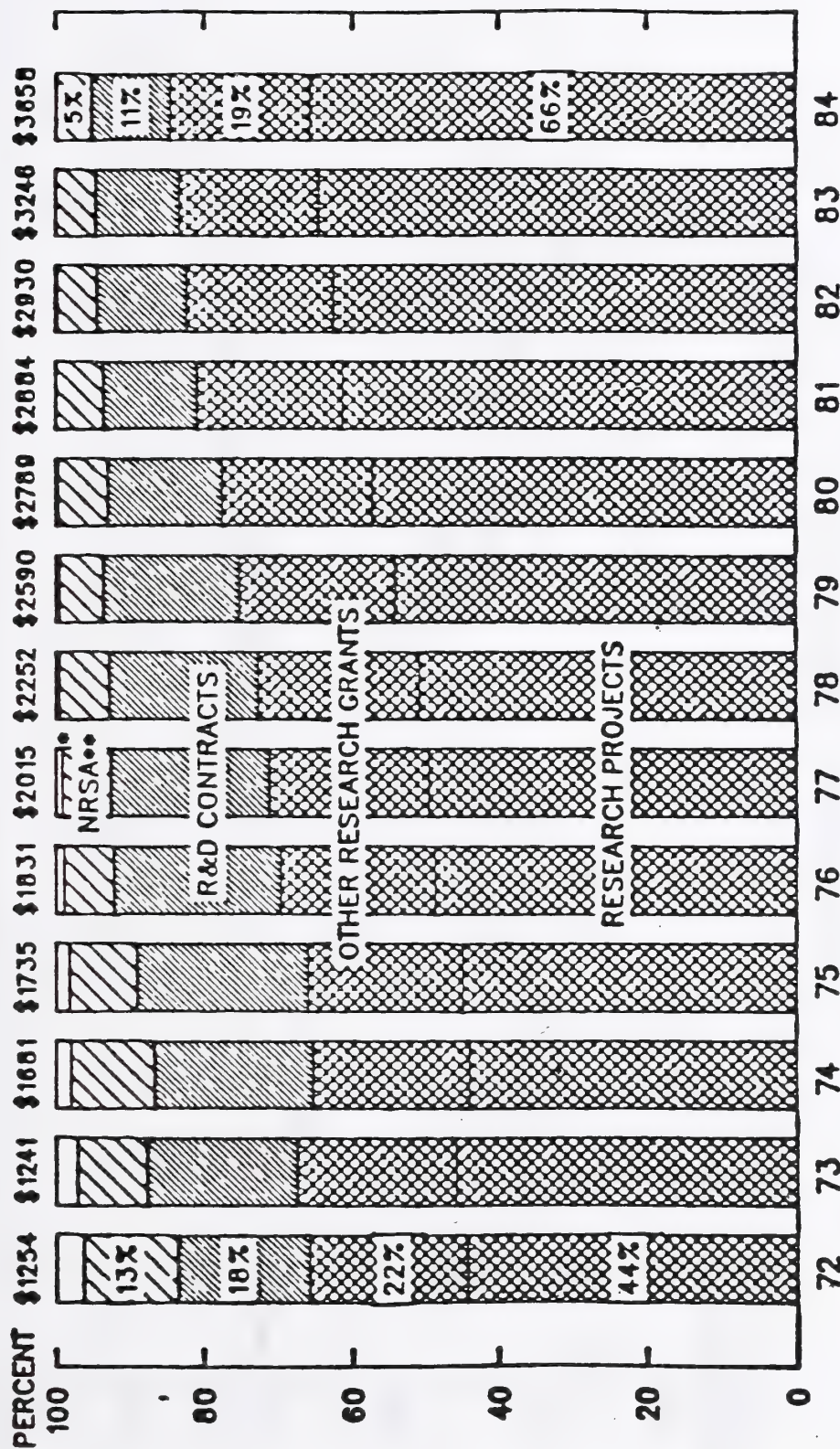
# Total NIH Appropriations, 1972-87, in Current and Constant Dollars (1972=100)

1 c.



2.

ALLOCATION OF NIH EXTRAMURAL AWARDS BY ACTIVITY, FISCAL YEARS 1972-1984  
PERCENT OF AMOUNT AWARDED (CURRENT DOLLARS IN MILLIONS)

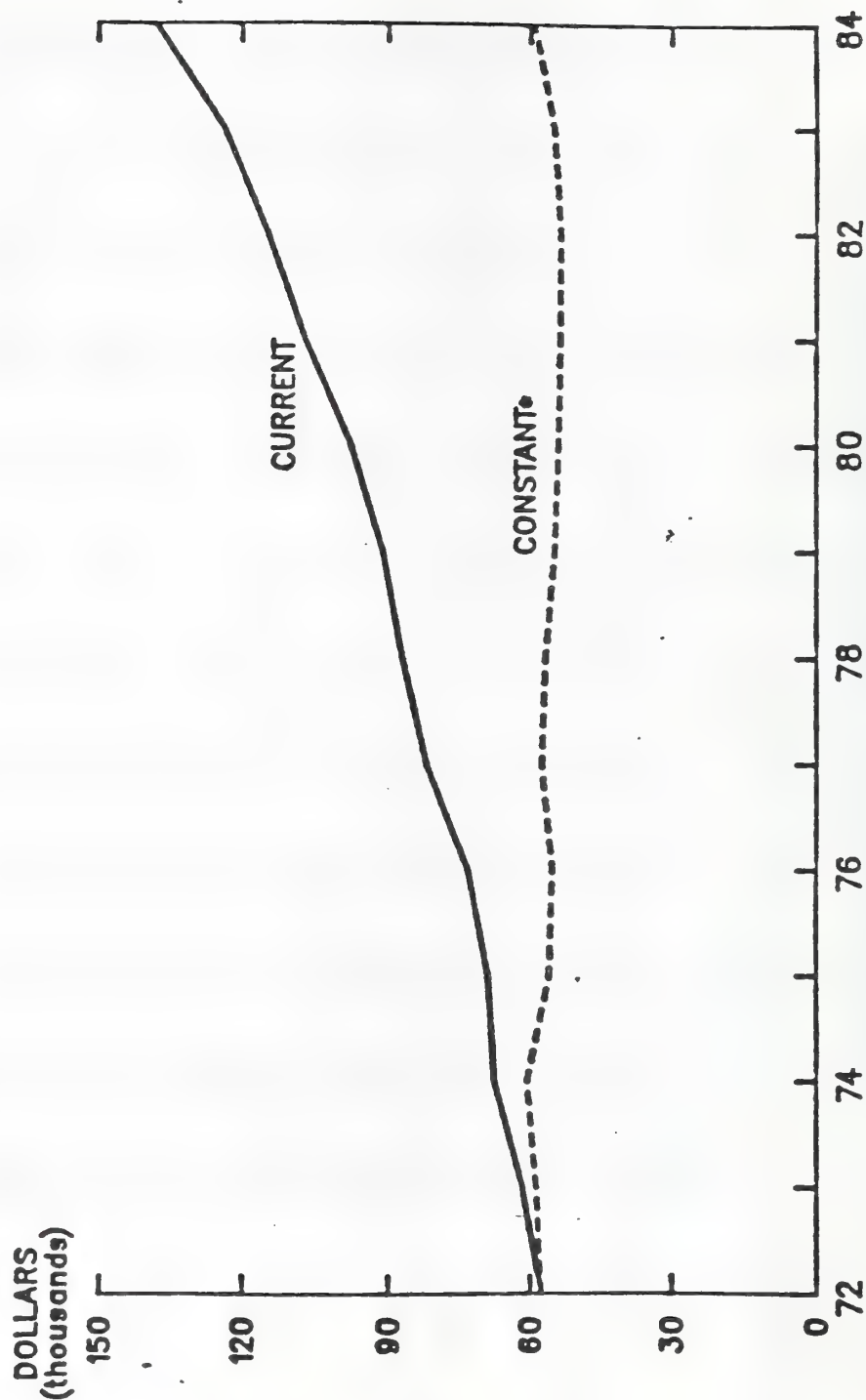


NOTE: EXCLUDES TO. \*INCLUDES CONSTRUCTION AND MEDICAL LIBRARY GRANTS. \*\*INCLUDES PRE-NRSA TRAINING.  
SOURCE: NIH, DOD, STATISTICS AND ANALYSIS BRANCH

79  
1/18/86



# AVERAGE DOLLARS FOR NIH RESEARCH PROJECT GRANTS FISCAL YEARS 1972-1984

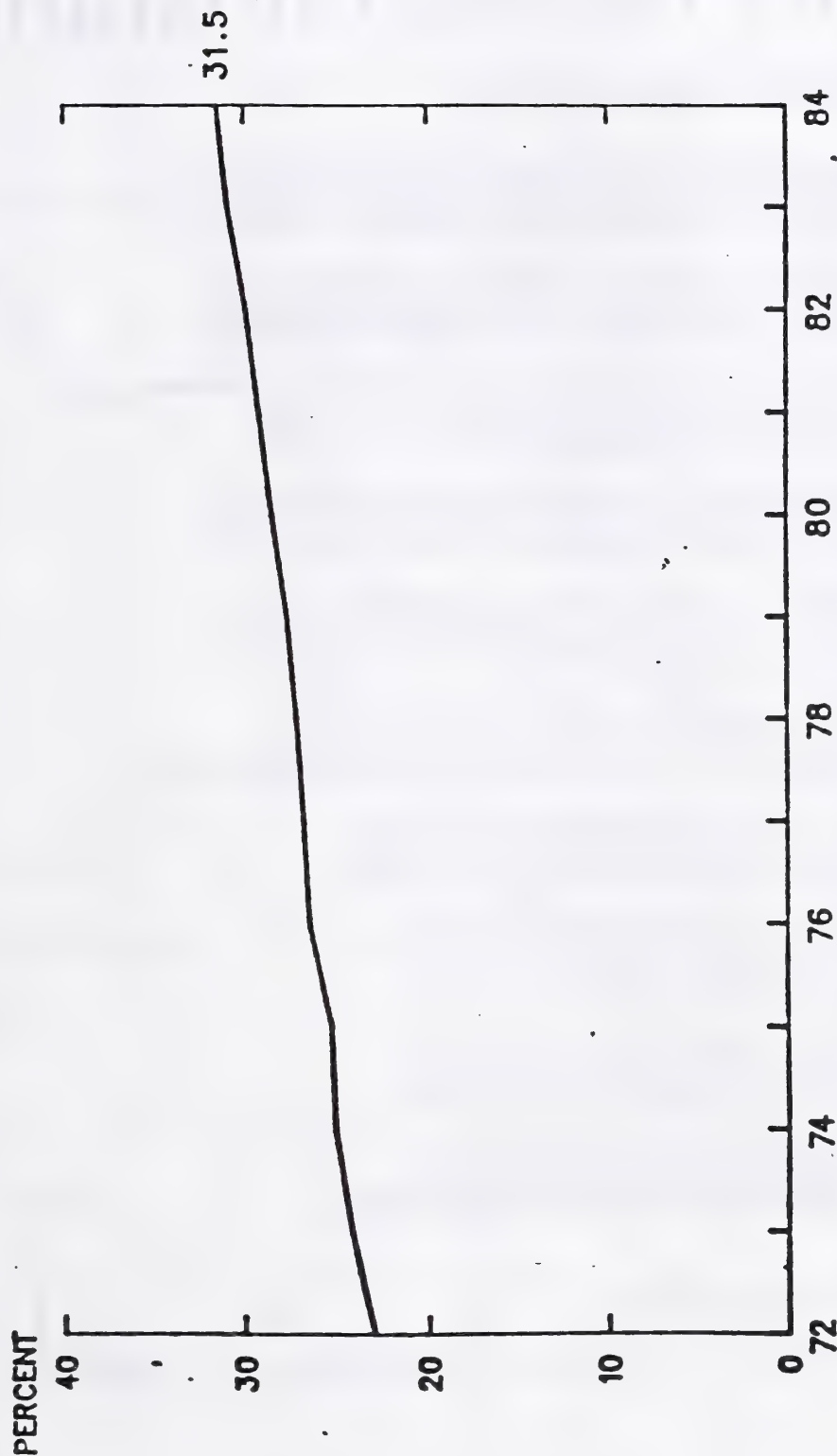


BASED ON BIOMEDICAL R&D PRICE INDEX FY1972=100.  
SOURCE: NIH, ORG, STATISTICS AND ANALYSIS BRANCH

K10  
4/18/88

Q. A.

# INDIRECT COST PROPORTION OF TOTAL COST\* FOR NIH RESEARCH GRANTS FISCAL YEARS 1972-1984

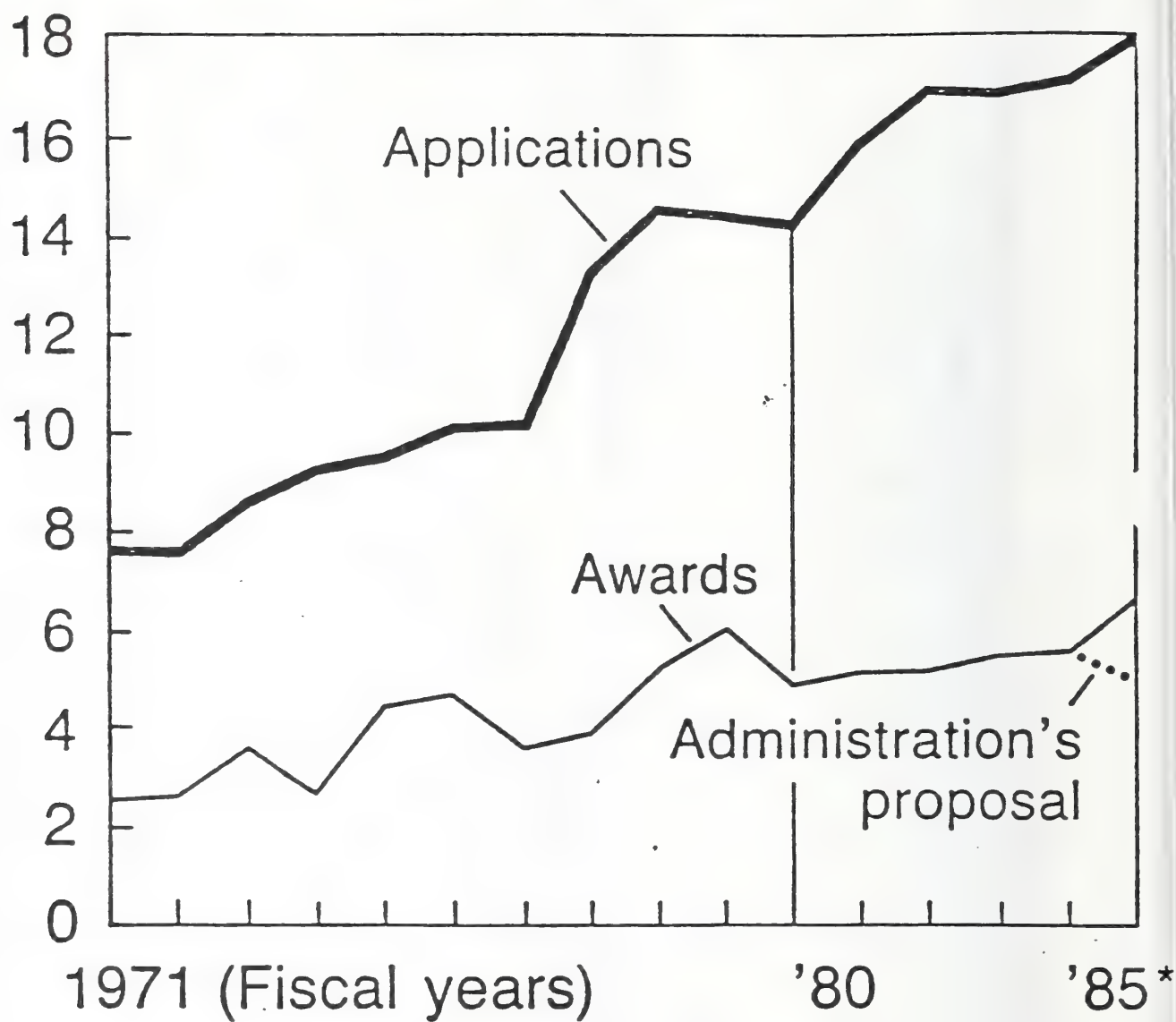


NOTE: EXCLUDES DRR, RCP AWARDS AND TO.  
SOURCE: NIH, ORO, STATISTICS AND ANALYSIS BRANCH

TS4  
4/10/85

Fig.

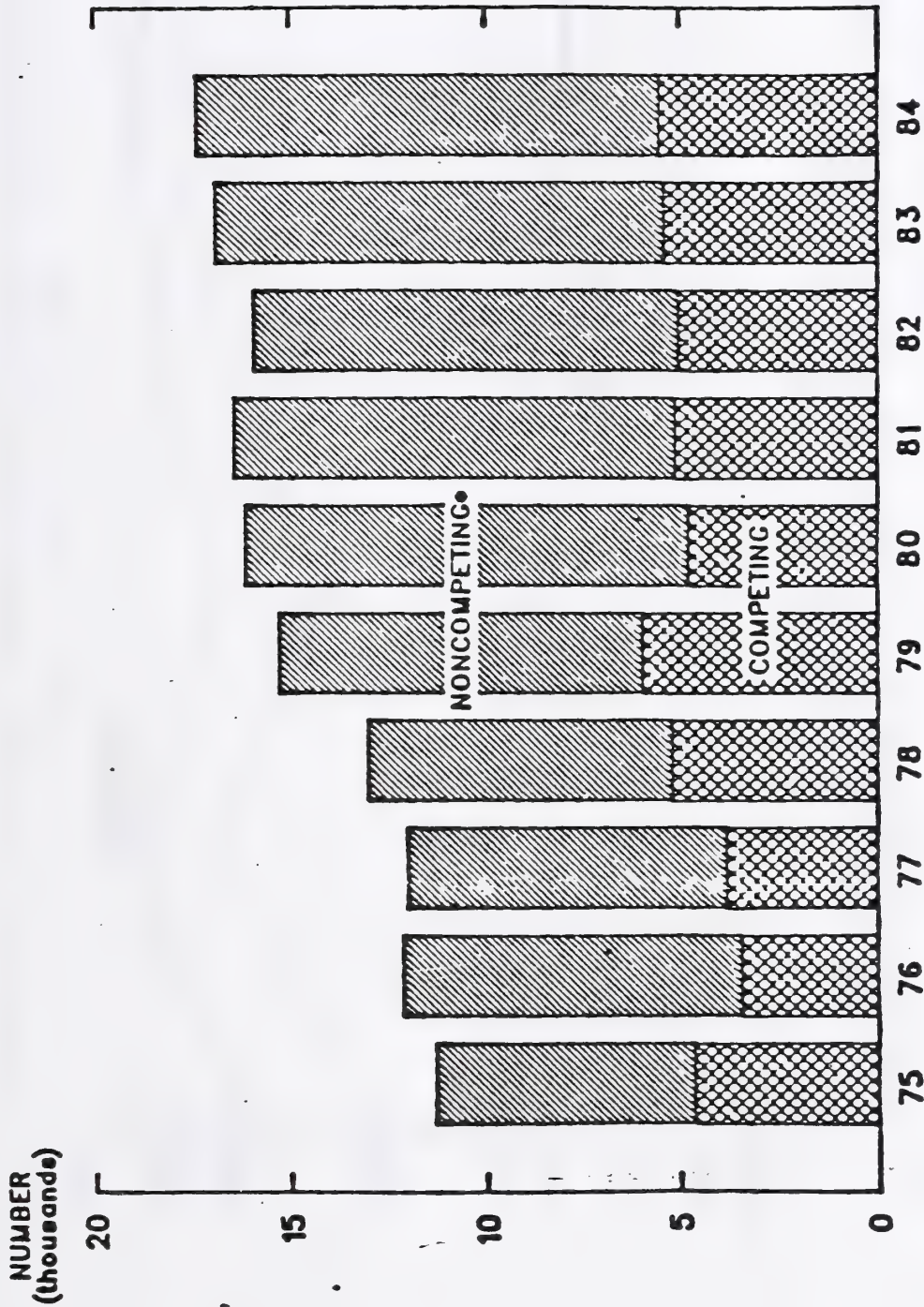
# NIH Research Grants (Thousands)



\*Projected

Source: National Institutes of Health

NIH RESEARCH PROJECT AWARDS  
FISCAL YEARS 1975-1984

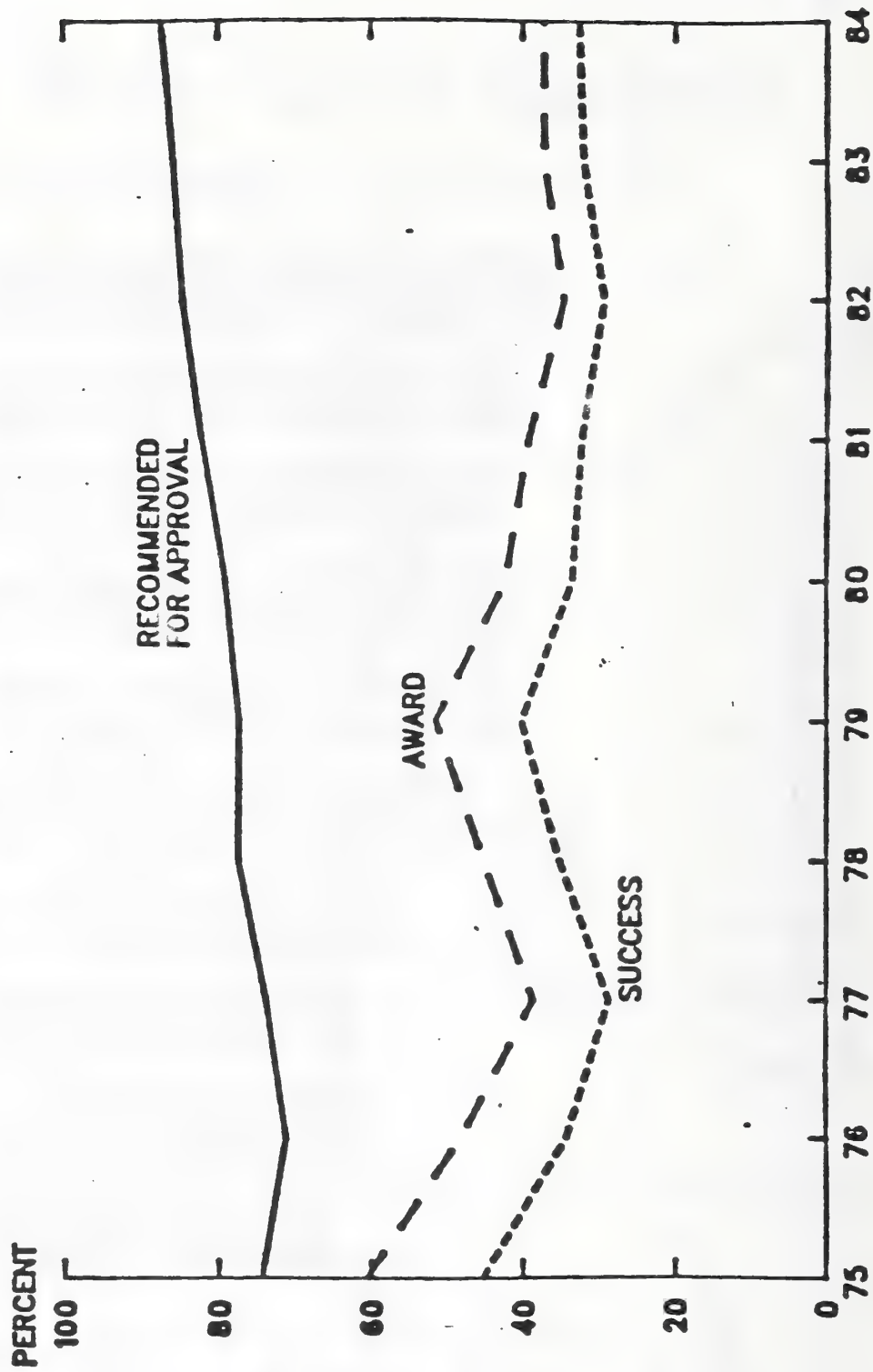


•EXCLUDES SUPPLEMENTS.  
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH



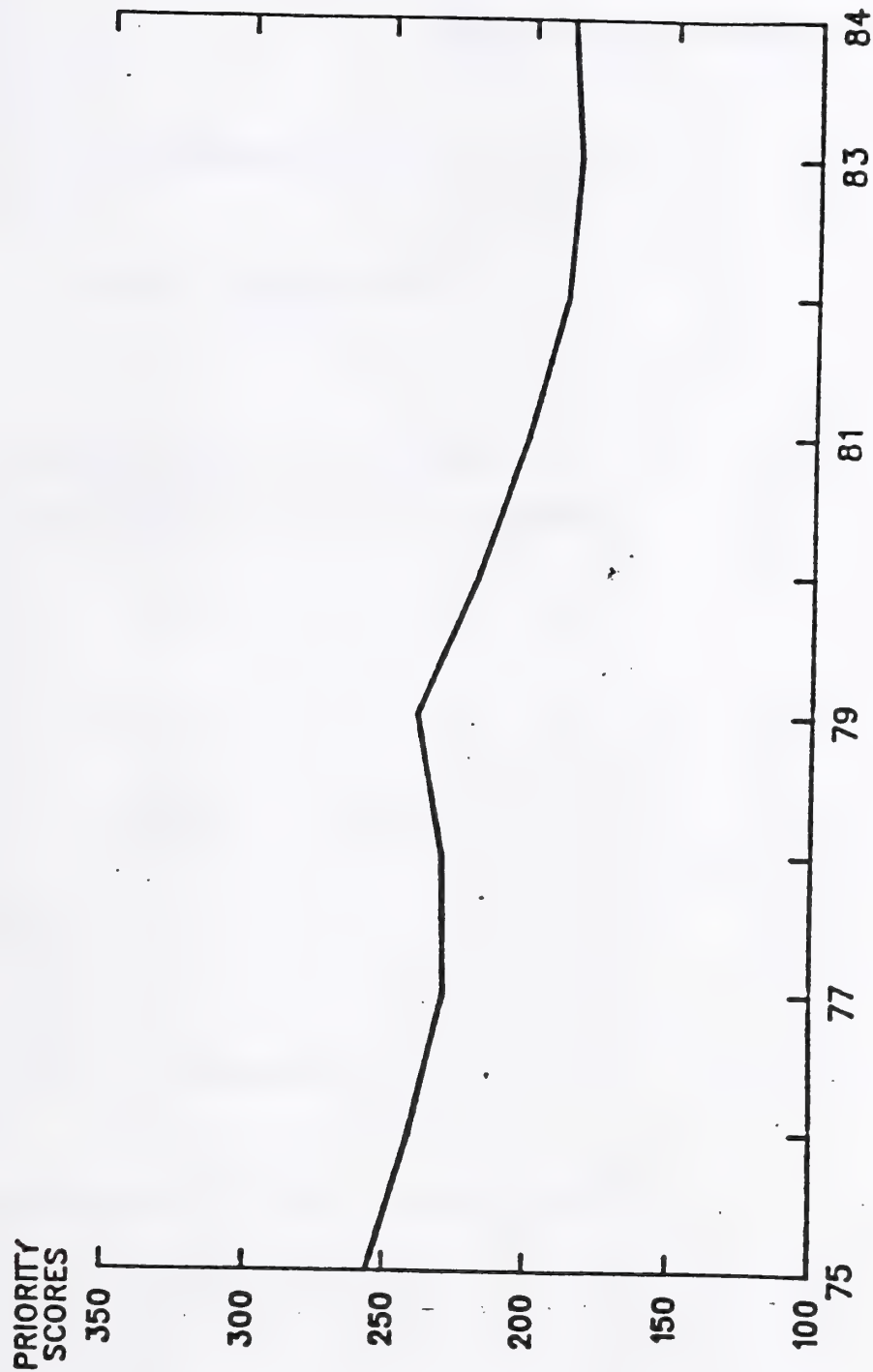
Fig. 1.

COUNCIL RECOMMENDED FOR APPROVAL, AWARD, AND SUCCESS RATES  
FOR NUMBER OF NIH RESEARCH PROJECT APPLICATIONS  
FISCAL YEARS 1975-1984



B. 2A.

: PAYLINES\* FOR NIH COMPETING RESEARCH PROJECT GRANTS  
FISCAL YEARS 1975-1984



\*NINETY PERCENT OF APPLICATIONS PAID IN A YEAR HAD PRIORITY SCORES BETTER (LOWER) THAN THAT SHOWN.  
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH



FOR RELEASE UPON DELIVERY

STATEMENT BY

JAMES B. WYNGAARDEN, M.D.  
DIRECTOR

NATIONAL INSTITUTES OF HEALTH  
PUBLIC HEALTH SERVICE  
U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

ON

SEAFOOD AND HEALTH

BEFORE THE

COMMITTEE ON COMMERCE, SCIENCE, AND TRANSPORTATION

UNITED STATES SENATE

APRIL 17, 1986



## SEAFOOD AND HEALTH

Mr. Chairman and members of the Committee, I am very pleased to have the opportunity to speak to you about seafood and health. This is an important topic addressed by several programs of the National Institutes of Health (NIH).

The possible association of increased intake of seafood with reduced incidence of certain diseases was first noted by epidemiologists. Epidemiologists are scientists who study patterns of disease in populations and the occurrence of particular associated factors-- environmental or behavioral--that might play a causative role in the disease.

First, consider the comparative amounts of fish eaten by various populations. For the Eskimos of Greenland, the average per capita fish consumption is about 14 oz. (400 g) per day. In Japan, the average per capita fish consumption is about 3 1/2 oz. (100g) per day, but consumption reaches 8-9 oz. (250 g) per day in areas where fish is part of the local economy. By contrast, fish is eaten less than four times per month by the average citizen in the United States.

Then consider that in the United States, the number one cause of death is coronary heart disease. By contrast, the death rates from coronary heart disease among the Eskimos of Greenland and among Japanese are low. Within Japan, the coronary heart disease death rate is higher on the mainland than on the Island of Okinawa and higher in farming areas than in fishing villages. These differences appear to be positively associated

with a higher fish intake of Okinawans compared with mainlanders, and of Japanese fishermen compared with farmers. These correlations appear to provide good reasons for the enthusiasm of epidemiologists who have documented the story of the relationship between disease patterns and fish consumption. Furthermore, similar associations have been seen with other disorders such as hypertension, asthma, and arthritis. I am going to discuss today the nutritional, biochemical, and medical evidence that explains how components in seafood may protect against several diseases. I will also share with you some of our thoughts about unanswered questions in this area and proposed research that might add to our knowledge of the relationship between seafood and health.

The beneficial factor in seafood that has captured so much attention of late is not found in the protein or in the carbohydrate of fish (fish has negligible carbohydrate), but rather in the fat. This fat or oil is rich in polyunsaturated fatty acids. Polyunsaturated fats occur in two major forms: omega-3 fatty acids, found in linseed and some seaweeds, and predominant in some fish and marine animals, such as salmon, mackerel, and seal, and omega-6 fatty acids, found in meats and poultry, and predominant in vegetable oils such as corn or soybean oil.

The omega-6 fatty acids that we ingest in vegetable oil can be metabolized in the body to arachidonic acid, and subsequently converted to many varieties of hormone-like substances such as prostaglandins, thromboxane, and leukotrienes -- also called eicosanoids. Overproduction of some of these eicosanoids seems to be involved in some diseases such as thrombosis and asthma.

## ROLE IN DISEASE PROTECTION

How might the omega-3 fatty acids so prevalent in seafood protect against disease? For heart disease, scientists offer several possibilities which are being investigated. The hypotheses relate to blood clotting or thrombosis; to changes in levels of blood cholesterol or blood triglycerides, or to the plasma proteins that carry blood lipids; to blood pressure; or to changes in the immune function. All are recognized risk factors that might promote the development of heart disease.

### Platelet Function

The first theory is that substances in fish oil reduce the tendency of blood to clot. This would result in less atherosclerosis and fewer strokes. Normally, when there is a blood vessel injury, platelets aggregate to stop the loss of blood from this area. This is followed by clot formation. The vegetable oil omega-6 fatty acids are used by the body to make arachidonic acid which is the precursor of prostaglandins. One of these prostaglandins, thromboxane  $A_2$ , stimulates platelet aggregation and eventually blood clotting. Fish oils provide eicosapentaenoic acid, which competes with arachidonic acid for the production of prostaglandins. In the presence of arachidonic acid, therefore, the blood will contain less pro-aggregatory substance, such as thromboxane, and more of anti-aggregatory material, such as the prostacyclins which are the most potent inducers of platelet anti-aggregation activity. The result could be prevention of excessive clotting.

## Lipids and Lipoproteins

Both the omega-6 and omega-3 families of polyunsaturated fatty acids reduce total plasma cholesterol and low density lipoprotein (LDL) levels. However, lipoprotein responses to these polyunsaturated fatty acids differ considerably. Unlike vegetable oils (omega-6), fish oils (omega-3) cause a dramatic reduction in plasma very low density lipoproteins (VLDL) and in triglyceride levels, particularly in patients with hypertriglyceridemia. The effect of fish oils on (LDL) and high density lipoprotein (HDL) levels has not been definitely established. However, in a number of recent dietary studies, which included fish oil as the major source of fat, LDL-cholesterol in normal individuals declined, and HDL-cholesterol was unchanged. These would be beneficial changes in LDL/HDL ratios, from the standpoint of cardiovascular disease.

## Blood Pressure

In addition to the biochemical effects on blood platelets and lipids, fish oil has also been reported to reduce blood pressure. Scientists have not yet ascertained the mechanism this effect, although an attractive hypothesis is that it is related to metabolic alterations in the prostaglandin biosynthetic pathways. Whether the effects are generalizable to all dietary polyunsaturated fatty acids or are specific for omega-3 fatty acids is also uncertain.



## Immune Response

Recent literature suggests that disorders resulting in circulating immune complexes worsen atherosclerosis. Examples of such exacerbation can be seen among patients with systemic lupus erythematosus, and arthritis. Experimentally, atherosclerosis has been exacerbated in both rabbits and nonhuman primates by the continued injection of antigens.

The mechanisms by which immunologic injury affects atherosclerosis remains unclear. Injury to the endothelium plays an important part in the development of acute and chronic vascular disease and associated thromboembolic complications. Blood components that interact at the injury site include platelets, blood coagulation factors, leukocytes, circulating immune complex, and other plasma proteins. Materials released from either the blood cells or the vessel wall at the injury site affect blood cells, the formation of thrombi, and the development of initial lesions. Although immune complex injury by means of deposition has been suggested, few studies have been conducted on the role that the immune complexes play in plaque formation.

Further work is needed to understand the interaction of omega-3 polyunsaturated fatty acids with the immune system as well as the influence of these acids on the movement and function of membrane receptors important in the immune functions.

## HIGHLIGHTS OF SOME RESEARCH PROJECTS RELATING TO DIETARY FISH OILS

The research community has become increasingly aware of the potential health benefits that may derive from increased consumption of dietary fish oils. It is important to remember that while research efforts have not focused heavily on this topic in the past, studies of dietary fish oils and their effects on blood clotting, lipid levels, and coronary heart disease have been underway for many years. Research into relationships between dietary fish oils and diseases other than coronary heart disease has only received significant attention within recent years. Let us look briefly at what those studies have shown.

Between 1956 and 1963, there were reports of seven studies of fish oil feeding in humans. The studies varied as to participants, the degree of dietary control, the sources of fish-oil fatty acids, and duration. In some, but not all, study participants, fish oils and vegetable oils were comparable in reducing levels of blood cholesterol. The principal intent of these studies was to demonstrate that polyunsaturated fats from any source (fish or vegetable) were effective in reducing levels of blood cholesterol. There was no indication from these studies that fish oils had unique properties not shared by other polyunsaturated oils from vegetable sources.

## Dietary Omega-3 Fatty Acids and Blood Lipid Levels

Up until 1983, six studies - four of which were the work of Dr. W.E. Connor and colleagues at the Oregon Health Sciences Center - reported observations in individuals with normal and with elevated blood lipids who were fed diets enriched with polyunsaturated fatty acids from salmon oil or with vegetable oils, compared with a control diet with relatively saturated fatty acid. This direct comparison of fish oil and vegetable oil diets provided the first evidence that omega-3 fatty acids possess properties for lowering levels of blood triglycerides not found in the polyunsaturated omega-6 fatty acids of vegetable oils.

Only a few studies have reported the effects of fish oils in patients who have elevations of blood cholesterol and triglycerides. In a study reported in the 1950's by Ahrens and colleagues in New York, both plasma cholesterol and triglyceride levels were reduced more by fish oil than by vegetable oil. Another study, reported in 1985 by Phillipson, Connor, and others at Oregon, indicated that LDL levels were lower and HDL were higher after vegetable oil diets compared with fish oil diets.

The effects of dietary fish oil on the plasma lipids of patients with severe hypertriglyceridemia were first reported in 1981 by Connor and associates. These patients, when consuming up to 30 percent of calories as fish oil, had a 77 percent drop in their triglyceride levels. By contrast, a diet containing 30 percent of calories as omega-6 fatty acids

caused such a rapid increase in the plasma triglycerides that the diet was stopped after 14 days. Thus, the omega-3 fatty acids appear to be of potential therapeutic benefit in patients with moderate to severe hypertriglyceridemia.

Dietary Fish Oil: Immunogenic - Cardiovascular Interactions;  
Atherosclerosis; and Hypertension

An NIH grant to the Oregon Regional Primate Center is supporting research on how diets based on lard, corn oil, or fish oil affect the health of mice and the progression of autoimmune and immune-complex disease and atherosclerosis. To date, it appears that the mice on the fish-oil-supplemented diet live longer and are healthier than the others. The study is continuing.

Several other researchers are studying the effect of dietary fish oil with the intent of clarifying the mechanisms of any beneficial or adverse effects related to atherosclerosis that might be mediated through factors such as plasma lipids, glucose tolerance, blood pressure, platelet factors, and cell membrane composition.

A study directed by Dr. Edwin Bierman at the University of Washington in Seattle seeks to understand, in humans, the mechanisms that account for reductions in plasma fats and cholesterol when individuals with normal or elevated blood lipids are fed omega-3 fatty acids. This



metabolic study is being conducted on an outpatient basis, with experimental diets supplied to the study participants. The project will assess biochemical and metabolic changes that are known to be related to the development of atherosclerosis such as blood lipids and blood clotting factors.

Scientists at the Vanderbilt University School of Medicine are studying the effects of dietary supplements of fish oils on the production of prostaglandins and leukotrienes in humans, and the role of these compounds in asymptomatic arteriosclerosis and mild hypertension.

#### Acute Pulmonary Disorders

Studying animal models and humans, Dr. Frank Austen at Brigham and Women's Hospital in Boston is evaluating the effects of dietary manipulation on respiratory physiologic responses to various stimuli. Respiratory responses to antigen challenge will be assessed following a diet enriched with menhaden fish oil, or a diet enriched with beef tallow.

Early data indicate that the animals fed the fish oil-enriched diet displayed less severe inflammatory responses associated with bronchoconstriction when challenged with aerosol antigen. It would thus appear that, in the animals studied, dietary supplementation with fish oil inhibited the bronchoconstrictor response. The beneficial effect of fish

fatty acids as measured by response to standard aerosol challenge has clinical significance, since asthmatic reactions in humans are precipitated by a similar challenge.

Dr. Austen and co-workers are also conducting a double-blind study to assess the effects on asthmatic patients of dietary supplementation with the fish oil component. It will be determined whether the patients receiving fish oil exhibit decreased inflammatory reactions in the lung, and thus avoid the pulmonary disturbances associated with asthma.

#### Need for Dietary Omega-3 Fatty Acids

Whether or not there is a dietary requirement for the omega-3 fatty acids remains an unresolved issue in human nutrition. Like the omega-6 fatty acid family, omega-3 fatty acids cannot be synthesized by animals and therefore must be provided in the diet.

Dr. William Connor and coworkers in Oregon are investigating the essentiality in non-human primates of omega-3 fatty acid during growth and development in an attempt to define the biochemical and functional consequences of omega-3 fatty acid deprivation. Female rhesus monkeys were fed semi-purified experimental diets which were either adequate or deficient in omega-3 fatty acids for a minimum of two months before conception and then throughout pregnancy with their infants receiving similar diets .

No significant differences were seen between groups in the mother's weight gain during pregnancy, the infant's birth weight, or the infant's body length or skull circumference at birth. However, the diet deficient in omega-3 fatty acid was associated with reduced levels of omega-3 fatty acid in skin and adipose tissue. Moreover, the omega-3 fatty acid deficient animals demonstrated visual deficits as measured by their impaired ability to adapt to darkness. Current studies are being conducted to determine the reversability of these findings as well as which omega-3 fatty acids can best be used to correct these abnormalities.

#### Anti-inflammatory effects of a fish oil enriched diet

Dr. Frank Austin and co-workers in Boston concluded from a study of several normal individuals who ate a fish oil supplemented diet that the fish oils derived from the fish oil had an anti-inflammatory effect. Inflammatory reactions are associated with rheumatoid arthritis, systemic erythematosus, psoriasis, allergic encephalomyelitis, and multiple sclerosis. Exactly how fish oil promotes an anti-inflammatory reaction is unclear. Although fish oils may diminish the release of prostaglandin derivatives that may in turn enhance antibody synthesis. However, it has been demonstrated that prostaglandins can have both anti-inflammatory and pro-inflammatory actions. Thus, there appear to be complex interactions of several systems that are influenced by dietary lipids. Scientists cannot as yet interpret the role of dietary lipids in these diseases.

Studies underway by Dr. Edwin Goetzl and colleagues in San Francisco indicate that fish oil given to normal individuals and asthmatics had distinct effects on several leukocytes (metabolites of prostaglandins) that might change the role of the mediators in asthmatics.

The research project of Dr. Dwight Robinson and coworkers (Massachusetts General Hospital, Boston, Massachusetts) is aimed at clarifying the role of omega-3 fatty acids and of prostaglandins and leukotrienes in inflammatory rheumatic diseases. A major approach of the research is to modify inflammation and immune responses by feeding omega-3 polyunsaturated fatty acids.

Previous work has shown that omega-3 lipids modify certain inflammatory and immune reactions in experimental animals. Dietary marine oils inhibit the development of autoimmune glomerulonephritis in lupus strains of mice. Dr. Robinson will investigate the effects of omega-3 fatty acids on other organ systems in murine lupus. In addition, the effects of these lipids on rheumatoid arthritis, acute hypersensitivity reactions, antibody formation, osteoclastic bone resorption, and the reactivity of pulmonary tissue to leukotrienes will be examined in animal models.

#### Severe Migraine and Omega-3 Fatty Acids

Investigators at the University of Cincinnati compared the effects of fish oil and a placebo vegetable oil in 15 persons with severe migraine in a double-blind, placebo-controlled trial to determine whether and how fish



oil would reduce severity of migraine. In individuals following the fish-oil-supplemented diet, there was a major shift in headache intensity toward the headache-free end of the scale. It is thought that the action of fish oil on migraine may be mediated through changes in prostaglandin synthesis and/or reduction in platelet serotonin release, with an overall decrease in cerebral vasospasm.

### Cancer Prevention

It has been generally observed that cancer risk is higher among people who consume diets high in fat and low in fiber, vegetables and some vitamins and minerals. Additionally, recent studies have demonstrated that not only the amount of fat, but the composition and type of fat influence the development of cancer.

Fats containing the omega-6 fatty acids which stimulate the production of immunosuppressive prostaglandins, are apparently favorable to the growth of tumor. Fish oil enriched diets decrease the production of these prostaglandins. In animal studies this coincides with retarded growth of tumor cells. In addition, fish oils contain high levels of vitamin A which can act as anti-neoplastic agents. Results obtained from recent experimental studies in animals suggest that fish oils and/or seafood-based diets may provide an effective non-invasive dietary intervention approach for reducing the risk of tumor growth and cancer.

### Some Current Research Plans

The NIH has plans to encourage and stimulate additional studies in omega-3 fatty acid research. As you know, the NIH issued, in December 1985, a program announcement, "Biological Mechanisms of Omega-3 Fatty Acids in Health and Disease States". Currently, three institutes have plans for initiatives in the forms of a program announcement, these include the (a) NIDDK to encourage research on the use of omega-3 fatty acids as a component of the structured lipid preparations used in parental nutrition (b) the NCI to encourage basic research studies on the role and mechanism of omega-3 fatty acids in cancer prevention and (c) the NHLBI to solicit research in omega-3 fatty acids and mechanisms of thrombogenesis and blood vessel atherogenesis.

Additional research on omega-3 fatty acids will be encouraged through the U.S./Japan Cooperative Medical Science Program. Also, the NIH has suggested omega-3 fatty acid research be included as a research priority in the Arctic Health Research Plan developed by the Interagency Arctic Research Policy Committee.

### RESEARCH NEEDS

Research on dietary fish oil consumption and its effects has been of interest to the biomedical research community for many years. Several pioneering studies have been undertaken in the field. Far from settling the issues, however, these studies have only pointed to the areas where

our knowledge is insufficient, and where further research is clearly warranted. We must thus focus our attention on how best to build upon the existing base of knowledge to clarify whether dietary fish oils do indeed have a role in preventing disease, and what types of research will best elucidate the fish oil-disease relationship.

We have interesting population findings that link fish consumption and disease occurrences. We can offer hypothetical explanations for the disease processes that involve metabolic products derived from fish oils. With few exceptions, however, we cannot yet define the fundamental biological mechanisms that might involve fish oil and lead to disease. We need better information on the amount of omega-3 or omega-6 fatty acids that induce specific changes in biological processes. We need to consider whether there is a desirable balance of omega-3 and omega-6 fatty acids in the average diet. Should programs aimed at lowering blood cholesterol levels and controlling levels of blood pressure strive for a balance in the types of polyunsaturated fatty acids? These are important questions and ones that I cannot answer today.

In summary, I hope this brief review provides a perspective on a recent and most active research area of the NIH. I will be pleased to consider any questions you may have.

# ROUTING AND TRANSMITTAL SLIP

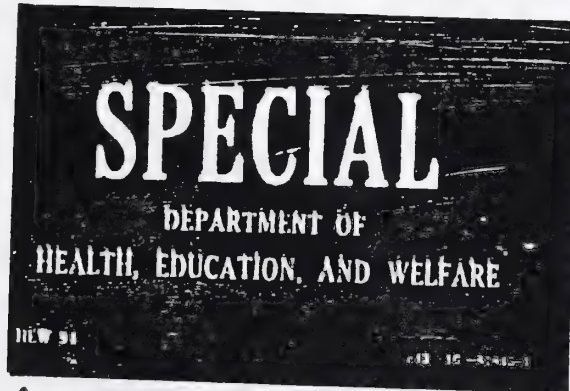
Date  
4/10/86

TO: (Name, office symbol, room number, building, Agency/Post)	Initials	Date
1. Dr. Wyngaarden		
2. Dr. Malone Dr. Beaven	Dr. Badman	
3. Dr. Go Dr. Knipmeyer	Dr. Moskowitz Dr. Korper	
4. Ms. Wolfle Ms. Feld	Ms. Houser Ms. Holcombe	
5. Dr. Hill		

Action	File	Note and Return
Approval	For Clearance	Per Conversation
As Requested	For Correction	Prepare Reply
Circulate	For Your Information	See Me
Comment	Investigate	Signature
Coordination	Justify	

## REMARKS

Your comments please by 3 p.m. Friday, April 11.



DO NOT use this form as a RECORD of approvals, concurrences, disposals, clearances, and similar actions

FROM: (Name, org. symbol, Agency/Post)	Room No.—Bldg.
Christina Blakeslee	207/1
Division of Legislative Analysis	Phone No.
	496-3471

5041-102

USGPO: 1984 O-381-529 (11M)

OPTIONAL FORM 41 (Rev. 7-76)  
Prescribed by GSA  
FPMR (41 CFR) 101-11.206





201

CERTAIN ASPECTS OF MEDICAL RESEARCH AND ITS SUPPORT\*

by

James B. Wyngaarden, M.D.\*\*

I am honored indeed to have been invited to participate in the celebration of the 600th anniversary of the founding of Heidelberg University. This great institution's influence is deep and pervasive throughout the western world. It is a symbol and embodiment of excellence. As an American I am impressed by recalling that the University was more than a hundred years old when Columbus began making his voyages of discovery.

It is with a certain humility--generated by my consciousness of the venerability of this institution--that I tell you that next year the National Institutes of Health (NIH) will celebrate its 100th anniversary.

The NIH came into being at a time when medical science in the United States lagged far behind the state of knowledge in Europe. Studies in the new discipline, bacteriology, led by Robert Koch and Louis Pasteur, were taking place in more and more European laboratories, but few Americans had participated in those advances. A yellow fever epidemic in 1878 had created widespread alarm in the United States and a variety of measures were proposed for its prevention and control--none particularly effective. Other communicable diseases, such as cholera and tuberculosis, were also matters of serious concern and because travelers and immigrants were thought to be bringing the diseases into the country, efforts to arrest the spread of contagion were concentrated at ports of entry. In 1887 a one-room laboratory was set aside in the Marine Hospital on Staten Island in the Port of New York. Called the National Laboratory of Hygiene, this modest facility ultimately became the National Institutes of Health.

---

\*Special Lecture presented at the 600th Anniversary Symposium at the University of Heidelberg, Germany, April 24, 1986.

\*\*Director, National Institutes of Health, Bethesda, Maryland

The laboratory was a fragile transplant from the fertile fields of European medical science. The German influence was frankly stated in a formal report to the Congress in 1888 by the U.S. Surgeon General who told of the founding of the NIH in these words:

"In August, 1887, a bacteriological laboratory was established in the port of New York.....The different apparatus supplied was modeled after those used in the laboratory of Dr. Koch, of the Imperial German Health Board, and is supplied with Zeiss's latest improved microscope objectives and microphotographic apparatus."<sup>1</sup>

An even stronger tie with European science existed in the person of the first director of the Laboratory, Dr. Joseph J. Kinyoun. Soon after establishing the hygienic laboratory, Dr. Kinyoun arranged for a six-month's assignment to two of the most famous medical laboratories in Europe, that of Dr. Robert Koch in Berlin, and the laboratory founded by Louis Pasteur in Paris. Dr. Kinyoun quickly made known to the U.S. Congress and the American people the importance of what was taking place in Europe, and enunciated his goal for the new institution. He stated that "this laboratory, situated and equipped as it is, should form the nucleus of one national in its character, and developed on the same line as those established in Germany, France, and England."<sup>2</sup>

For the first 50 years of its history, the newly established agency continued as essentially an independent, freestanding laboratory of limited size. It was moved to Washington before the turn of the century and in 1930 was renamed the "National Institute of Health."

The modern era of the NIH, as well as that of biomedical research in our country, began when the Government and non-Government research laboratories, mostly in academic institutions, joined their efforts in carrying out research during World War II. Our Nation's response to the challenges of war included the formation of productive partnerships between the Government and academic institutions, as well as independent laboratories for the conduct of biomedical research. To meet the urgent need for additional knowledge on how to deal with the health problems of the armed services, the government turned to the established non-Federal laboratories

for help in conducting vital research. Grants and contracts were awarded for the support of such essential investigations. The arrangement worked exceedingly well. The newly formed partnerships greatly accelerated progress in research and development across the spectrum, from the most basic research to studies on the widespread application of newly formulated measures for prevention, diagnosis and treatment of disease.

By the end of the war the U.S. Office of Scientific Research and Development was administering a large number of medically related research projects. A leading American scientist, Dr. Vannevar Bush, the President's science advisor, urged that the Government continue to support the medical research then underway in many universities and hospitals. After Dr. Bush's proposal was accepted, the National Institute of Health was given the responsibility to administer the ongoing projects. This peacetime collaborative effort represented a significant change in national policy--it was a frank recognition of the mutual benefits to be realized from such a partnership.

In a report written in 1945, titled "Science--The Endless Frontier," Dr. Bush outlined the new policy that has served the National interest so well in succeeding years. In recommending that the Government continue to support research in non-Federal laboratories, he asserted that: "The publicly and privately-supported colleges, universities and research institutes are centers of basic research. They are wellsprings of knowledge and understanding. As long as they are vigorous and healthy, and their scientists are free to pursue the truth wherever it may lead, there will be a flow of new scientific knowledge."<sup>3</sup>

To justify this recommendation, Dr. Bush pointed out the close connection between improved medical care and research. He said that, "While additional physicians, hospitals and health programs are needed, their full usefulness cannot be attained unless we enlarge our knowledge of the human organism and the nature of disease. Any expansion of medical facilities must be accompanied by an expansion of medical training and research."<sup>4</sup> Dr. Bush was careful, however, to emphasize that in the course of supporting research and training the Federal Government should not



interfere with the freedom and integrity of academic institutions. Specifically, he recommended that government grants should allow complete independence and freedom for the scientist to determine the nature, scope, and methodology of his or her investigations. "Scientific progress," he said, "results from the free play of free intellects working on subjects of their own choice, in the manner dictated by their curiosity for exploration of the unknown."<sup>5</sup> It is on this philosophical foundation that the research support programs of the National Institutes of Health were established and have continued to flourish.

The key instrument that NIH has used to provide support for biomedical research is the project grant, each made to fund an investigator-initiated project proposed to the NIH by an individual scientist. This type of grant is the mainstay of the NIH programs. In 1986 more than 57 percent of the total NIH budget of over \$5 billion is devoted to such project grants. We believe that they foster creativity and excellence, and are an effective instrument for involving our country's finest scientists in the National effort to improve health through the advancement of knowledge.

As far back as the 1940s, there was recognition that a critical element for progress in science is the success of our effort to assure a continuing renewal of the body of first-class scientists who can and will put their creative energies to the search for new knowledge. At the heart of many of our policy considerations in the 1940s, during the intervening years, and just as strongly at present, is the concern that somehow we must make careers in research attractive and feasible for the best of the generation now setting the course of their careers. I will return to this theme.

In the short period of five years from 1940 to 1945 the NIH changed from a small Federal laboratory, whose activities were almost entirely in-house, to an agency whose focus turned increasingly to the support of research in non-Federal institutions. Addition of the extramural dimension to the NIH was accompanied by increases in budget--increases that have been spectacular. In terms of purchasing power in constant dollars, the total budget of NIH grew from 1945 to 1968 at an astounding average rate of 24

percent per year. The growth per year since 1968, taking inflation into account, has been much less--about 2 percent per year.

The extremely rapid growth of the budget in the earlier period resulted, in part, from expansion of the scope of the agency through the creation, one by one, of new institutes. There are now 12 institutes, most of them oriented to specific organ systems or to families of diseases, as for example, the National Heart, Lung, and Blood Institute, the National Eye Institute, the National Cancer Institute, and the National Institute of Allergy and Infectious Diseases.

Changes in the NIH budget in more recent years have tended to be selective with some programs enjoying substantial increases as compared with others. But in the main, the changes have represented efforts to make our programs more effective through adjustments in the proportion of funds assigned to such categories as project grants, contracts, intramural research, etc. The salient feature of these adjustments was the marked shift in the allocation of funds to favor the support of grants for investigator-initiated projects. In the period from 1972 to 1984, the budget for research project grants increased from 44 to 66 percent of the extramural budget. There was a compensating reduction in budget for contracts as well as for training grants.

After 1979 when our budget began to decline in real dollars because of inflation, and we had made all feasible shifts among program mechanisms, it was decided that the highest priority must be given to the maintenance of a relatively stable and predictable number of investigator-initiated grants. We recognized that to assure continued research progress and thus future health gains, the Nation's research capability must be sustained and enhanced. As applied to investigator-initiated grants, a major goal is to minimize year-to-year fluctuations of funds available for the new and competing renewal awards. The average grant award is made for a period of from three to four years, and a grant may be renewed if the renewal proposal is successful in competition with other renewal applications as well as new proposals. Thus, the amount of funds available for new and competing renewal awards is an index of opportunity from the viewpoint of the

investigator. Our effort to maintain an adequate and predictable level of funding for new and competing renewal awards has been called in government jargon the "stabilization initiative."

The initiative has been an important element of the NIH budget for the past seven years. I will not go into further detail regarding it other than to say that its purpose is not only to undergird the investigator-initiated project grant as the prime means for supporting research, but also to reassure young investigators by demonstrating to them that even in a time of budget restraints research careers are not restricted to the very few.

The NIH provides support for research training through a variety of types of grants. Currently, more than 10,000 trainees are being supported through our different training programs at academic medical centers, research hospitals and laboratories throughout the United States.

Additionally, at the site of our headquarters in Bethesda, a highly effective training program is conducted in our own laboratories and clinics. I have not previously discussed our on-campus or intramural research program, and a few words regarding these programs are appropriate in the context of our training activities.

About half a billion dollars, more than 10 percent of our total budget, will be used this year for research in NIH's own laboratories. About 2,500 scientists with doctoral degrees and as many as 3,500 trained support staff are engaged in our intramural research program. The diversity of the program was described recently by one of our senior scientists, Dr. Maxine Singer, who told an audience of industrial scientists that "on the campus, we are divided up into all manner of units, some with targeted goals, some with total scholarly freedom, some with clinically oriented concerns, some with interests in basic biology that cover the gamut of living organisms and the whole range of biologically relevant questions from the synthesis of important organic molecules, computer applications, through the development of fly embryos, and the treatment of major diseases."<sup>6</sup>



Research training is an essential and integral part of our intramural research activity. We offer a variety of structured experiences for postdoctoral trainees in graduate and professional level programs in the clinical and basic sciences. At this time 886 trainees are participating in our regular training programs.

Above and beyond the regular training programs we conduct the NIH Visiting Programs for talented scientists from throughout the world, who come to Bethesda to share in the resources of the NIH. Through this program distinguished scientists at all levels of their careers are invited to receive further training or to conduct research in their biomedical specialities. Stipends are provided and each participant in the visiting program works closely with a senior NIH investigator who serves as sponsor or supervisor during the visitor's period of award or appointment. Currently over 1,100 scientists from 70 countries are participating in our visitors' programs, including 31 from the Federal Republic of Germany.

About 400 guest workers also participate in research at the NIH. These scientists do not receive stipends but are provided laboratory space and research support. Currently 33 of our guest workers are from the Federal Republic of Germany.

In a number of ways our visiting program resembles the international fellowship programs conducted by the Alexander Von Humboldt Foundation that supports qualified biomedical scientists who come to the Federal Republic of Germany to carry out or collaborate in basic or clinical research. The NIH acts as a contact point for American scientists interested in participating in the Von Humboldt program.

In whatever setting research training takes place the flow of young people through the laboratories exerts a powerful influence. The trainees with their imaginative and probing minds provide the kind of challenge to senior scientists that graduate students offer in a university setting and their presence is an essential element in a continuous process of renewal for our staff scientists.



Permit me to return to the more general theme of the Federal-private partnership for biomedical research in the United States. Concurrently with and in large measure as a result of the development of Government-medical school partnership, there has been amassed a spectacular store of biological knowledge, not to mention tremendous advances directly relevant to human health--particularly those advances that can be said to have ushered in the age of molecular biology. Clearly the era was in part spawned by the Government/academic partnership. This is demonstrated by the fact that of the individuals who have been honored by the Nobel Prize for these seminal discoveries in basic genetics, a substantial number were Americans, and the majority of them worked in institutions involved in Federal/academic partnerships under NIH programs. One was an NIH intramural scientist. The major stimulus for this type of research, of course, was the proposal in 1952 by Watson and Crick of the "double helical" structure of DNA, which offered powerful suggestions about the mechanisms of mutation and replication. The actual discoveries of the other Nobelists of the genetic research coterie were important, but of even more consequence was the epoch they engendered with their research tools and methodology. The succession of germinal advances in molecular biology resulted primarily from their use of very simple systems--bacteria and viruses as the basis for their studies.

This reductionist approach has had a profound effect upon research that is not frequently perceived--it has blurred the lines between the once inviolable territories of the biomedical disciplines. There has been a coalescence in language and in the techniques and methodologies of biochemistry, genetics, virology, microbiology, physiology and even anatomy with the common language being that of chemistry. The knowledge gained in the area encompassed by the term molecular biology has expanded so greatly during the past 30 years that some say it is beginning to disappear as a separate entity, reduced to chemistry on one level and expanded into cell biology on another.

We may no longer know what to call these new scientists--molecular geneticists, molecular biologists, biochemists, or virologists--but it is clear that there is ample scientific opportunity for them to expand their

spheres of interest. The era of science heralded by the discoveries in genetics in the 1950s and the 1960s has provided the broad field of biology with a set of unifying principles and properties that can be tested in almost infinite variety.

The biological revolution is far from over, and in fact is beginning to approach major questions with immediate relevance to human health. Recombinant DNA techniques have made it possible to produce human insulin in commercial quantities. In fact, this product is now on the market in our country. Another is recombinant human growth hormone, a superior substitute for the rare and expensive product derived from human pituitary glands. Recombinant gamma interferon for use against cancer and viral infection, and a substance called tissue-type plasminogen activator--a blood clot dissolver for coronary patients--are in clinical trials. Agricultural and food processing application of the new techniques are in the offing.

A remarkable and largely unanticipated aspect of biotechnology has been its diverse impact and potential for bolstering the economy. In the United States it is estimated that there are at least 200 small companies specializing in biotechnology, and many large chemical companies are conducting recombinant DNA research. It is estimated that future sales of biotechnology products will reach between \$20 billion and \$100 billion annually by the year 2000.

But what can be overlooked in all the excitement about applying biotechnology is the solid foundation of basic research in the life sciences that undergirds these current efforts. Most of the fundamental scientific advances that proved to be crucial to the evolution of biotechnology were made at universities and medical schools around the country, supported largely the the NIH.

The NIH became involved in policy formulation for the conduct of this new science long before the term "biotechnology" was a part of our everyday language. Back in 1973, when few--certainly not the general public--knew very much about the promises and potential perils of recombinant DNA

research, scientists working in the field requested a voluntary "moratorium" on such gene-splicing work while questions of safety were further evaluated. They also proposed that the NIH devise guidelines to be followed by investigators working with potentially hazardous recombinant DNA molecules.

Impelled by public, scientific and congressional pressure attending the matter, the NIH--which traditionally has shunned a regulatory role--rather reluctantly took on responsibility for organizing a mechanism for setting safety guidelines. The Recombinant DNA Advisory Committee, initially made up of non-Federal advisors--mostly scientists--was established to develop proposed guidelines for recombinant DNA research carried out with NIH funding. Following a great deal of public discussion and comment, guidelines were produced that were designed to permit research to continue with minimal constraints, yet to protect the public interest.

The new guidelines served to relieve public pressure on the issue. There were still a few unfortunate newspaper, magazine and television articles about the potential dangers of such research, and some local communities voted to exclude all such research in their localities. But for the most part, the public began to focus on the potential benefits of this type of research.

But by no means are all policy issues involving the future of recombinant DNA research and application settled in the United States.

Although biotechnology began in the biomedical area, it is valuable for a multiplicity of other applications, and from there some new problems have arisen. One current issue is debate over the safety of the release of DNA recombinant materials in the environment in connection with field testing of bacteria genetically engineered to protect plants from different problems such as frost damage or from insect pests.

A second current issue is human gene therapy using genetic engineering techniques. At the same time that policy issues surrounding field testing of agricultural products are being refined, policy formulation for gene therapy research proposals is moving steadily forward. Recently the NIH



Recombinant Advisory Committee developed and published a document entitled "Points to Consider in the Design and Submission of Human Somatic Cell Gene Therapy Protocols" for the guidance of scientists considering gene therapy research in human subjects. The research covered in the document involves transplanting genes into a patient's body cells to correct an otherwise incurable disease, in what is defined as somatic cell gene therapy. The document approved by the Advisory Committee specifically excludes any experimental treatment that is designed to produce effects that could pass from one generation to the next.

The publication of the guidance from the Recombinant Advisory Committee is an important step in bringing gene therapy into practical use, and will permit the several scientific teams studying gene therapy to propose specific trials with patients.

Another policy matter related to biotechnology is indicative of the broad potential of this field. Because the products of biotechnology are so diverse, their development and use in many instances fall within the regulatory authority of Federal agencies such as the Environmental Protection Agency, the Food and Drug Administration, or the Department of Agriculture. A government-wide framework for coordination of biotechnology has been established under an interdepartmental Biotechnology Science Coordinating Committee to assure that the production and application of these fruits of research are not only encouraged but also carried out with necessary concern for the public interest.

Publicly-supported agencies must be accountable to the public. Neither the circumstances nor common sense allow the scientific community to disregard widely held public concerns even though they may emerge from incomplete or erroneous information. Scientific institutions, particularly Federal agencies, have a responsibility to improve the public's understanding of biomedical research, its problems, its possible hazards and, of course, its benefits. The NIH's experience in dealing with the public's initial alarm about recombinant DNA techniques convinced us of the necessity for open discussion. Although the technical presentations and arguments were understood by few of the general public, the very fact that we were willing



to discuss issues and questions fully and openly generated confidence that our scientists were, indeed, concerned about more than their science. There was a perceptible and lasting easing of tension about recombinant DNA when it was perceived that we would maintain such openness.

Permit me to turn to another issue. In the recent past, the United States and the countries of Western Europe have seen a resurgence of a chronic public policy problem affecting biomedical research--a revival of antivivisectionist fervor.

It is easy for the public to forget that an important element behind medicine's success story is the laboratory animal. During the past century, virtually every development in biomedical research has depended at some point upon the use of animals.

Scientists and physicians at many institutions in the United States are coming under pressure from a small but determined segment of activists. There have been break-ins at about a dozen sites and a sit-in at the NIH. At other institutions there have been bomb threats and vandalism against the property of investigators and others associated with studies requiring animals. It is obvious that serious attention must be given by the scientific community to the issues that have been raised by the so-called animal rights groups. The NIH is now conducting what amounts to a comprehensive review of the use of animals in all of our funded programs. We have published new guidelines, stricter than the previous ones, and are requiring all institutions where we fund research to provide us with assurance that they are in compliance with the new guidelines. We are intensifying our review of research proposals considering not only the scientific merit, but also the feasibility and propriety of the kinds and numbers of animals proposed for use in the research plans. We are also endeavoring to sensitize program personnel and reviewers to the sometimes overlooked but important factor of "social acceptability" of proposed research.

In a real sense, the "social acceptability" and the public's perception of the value of everything we do has a direct influence on the funding of

our agency. The annual budget of the National Institutes of Health is decided upon each year by the U.S. Congress. Their decisions are made after a series of hearings at which we explain and justify the President's budget estimate for the coming year. The President's budget is the end product of many months of internal planning, refinement, discussion, and in some instances confrontation. Development of the budget is a distillation of hundreds of plans and decisions regarding those plans. During March this year the heads of the principal components of the NIH appeared before the appropriations committees of the U.S. House of Representatives and the Senate to explain and defend their portions of the approximately \$5 billion request by the President on behalf of the National Institutes of Health.

I used the word "defend" deliberately, for one of the basic rules and traditions regarding budgetary procedure is that once the President has presented his budget request to the Congress it is our proper role as program heads to defend and not to subvert the process by special pleadings. As a result we sometimes have the surprising spectacle of a department head whose budget has been cut drastically, refusing to admit that his agency has been wounded and repeating to the Congress the rationale for the cuts, a rationale that only a few months before he had bitterly opposed in the inner councils of the Administration.

President Harry Truman wrote a policy on this subject that has been reaffirmed by each succeeding President. Almost every year just before the congressional budget hearings, agency heads are reminded of President Truman's memorandum in which he stated "...I cannot condone the practice of (agency heads) seizing upon any opportunity which presents itself to indicate an opinion either directly or indirectly that my estimates are insufficient." He then stated the order in positive terms. "I shall expect (agency heads) and their subordinates to support only the President's estimates in hearings and discussions with members of Congress."<sup>7</sup>

These 1946 instructions have been reaffirmed by every President since. But citizen witnesses are not bound by the discipline that applies to agency officials and they are free to make appeals for increases of funding for any particular program in which they have interest. The Congressional

Appropriations Committees each year invite citizen witnesses to appear and comment on the Administration's current budget proposals. Leading scientists, educators and representatives of professional and lay organizations concerned with health matters use this opportunity each year to impress upon the Congress the vital importance of funding biomedical research. For the past few years a coalition of scores of organizations has developed annually its alternative budget for the NIH and has advocated strongly its approval.

Over the years a pattern has developed with respect to the NIH budget that differs from the treatment given to most other Federal agencies. Almost without exception, for more than 30 years the Congress has annually appropriated more funding for the National Institutes of Health than had been requested by the President. Some believe that successive Administrations have trimmed their requests for an agency in anticipation of increases by congressional action.

It is gratifying that the people of the United States, acting through their elected officials, are willing to continue to invest substantially in biomedical research.

This gives us confidence that as we mark our centennial, celebrating "a century of science for health," we can look forward to continued and accelerating progress.

REFERENCES

- <sup>1</sup>Furman, Bess, A Profile of the United States Public Health Service 1798-1948, U.S. Government Printing Office, Washington, DC, 1973, p. 196.
- <sup>2</sup>Furman, Bess, A Profile of the United States Public Health Service 1798-1948, U.S. Government Printing Office, Washington, DC, 1973, p. 203.
- <sup>3</sup>Bush, Vannevar, Science The Endless Frontier, report to the President on a program for postwar scientific research, 1945, p. 7.
- <sup>4</sup>Bush, Vannevar, Science The Endless Frontier, Report to the President on a program for postwar scientific research, 1945, p.9.
- <sup>5</sup>Bush, Vannevar, Science The Endless Frontier, Report to the President on a program for postwar scientific research, 1945, p. 7
- <sup>6</sup>Singer, Maxine, an unpublished address delivered at the NIH Symposium for Scientists From Industry, November 21, 1985, p. 3.
- <sup>7</sup>Truman, President Harry S., memorandum to the Director of the Bureau of the Budget, November 15, 1946.





## REMARKS\*

By

James B. Wyngaarden\*\*

It is an honor and privilege to accept this award from the NDRI on behalf of the National Institutes of Health. When I say the National Institutes of Health it is exactly what I mean for, as you all know, every one of the 12 NIH institutes support programs and projects relating to diabetes--the original concern of the NDRI--and to the NDRI's expanded interests. Our Division of Research Resources, too, has a special type of mission relating to these research efforts.

All of you are aware that the categorical boundaries of institute lines are porous and permit the free flow of scientific knowledge. This is particularly important in diseases such as diabetes where nearly every body organ and tissue is affected. Your meeting to follow today clearly recognizes the importance and advantages of this kind of cross-fertilization and sharing of basic knowledge, techniques, resources and scientific methods.

---

\* To receive an award from the National Diabetes Research Interchange Hyatt Regency Hotel, Bethesda, Maryland, April 30, 1986.

\*\* Director, National Institutes of Health.

240

In my view, this recognition has brought us a long way in diabetes and other disease areas. As an example, our major successes in the last 20 years or so in diabetes-related problems in large part have been due to the support of fundamental work, applicable to many diverse disease entities. We saw a great burst of progress at a time when ongoing scientific research had laid a foundation of basic understanding of physiology, genetics, and immunology. The tools needed to attack the questions posed by diabetes were there. In just the last decade, scientists in the diabetes field have capitalized to the fullest on these understandings and resources. As a result, the growth in recent years of our understanding of diabetes has been unprecedented. The same could occur with other disease areas as well.

As is true of most important endeavors, success lies closer when all concerned work cooperatively. This has always been the case with the NIH and the NDRI and fellow voluntary organizations. I feel sure that in years to come, this spirit will carry us well beyond the half-way point in diabetes and offer the same hope in other disease areas.

## TASK FORCE ON SCIENCE POLICY

### Hearing on THE FUTURE OF THE NATIONAL ACADEMIES

May 6-8, 1986

#### STATEMENT OF PURPOSE

The purpose of this portion of the Science Policy Study is to examine the future role of the National Academies in providing scientific, technical, and policy advice to the Federal Government. The review will encompass the National Academy of Sciences, the National Academy of Engineering, the National Institute of Medicine, and their operating arm, the National Research Council.

In order to conduct this review the Task Force will seek answers to the following questions:

1. How have the academies fulfilled the original mandate of the Science Academy's Congressional Charter to "whenever called upon by any department of the government investigate, examine, experiment, and report upon any subject of science or art...."
2. In what manner and how effectively does the advice provided by the academies meet the needs of government agencies asking for it, and can that advisory process be improved upon? Will the process of utilization change in future decades as the character of American science evolves and the needs of the government change, and if so, how?
3. On science and technology issues which overlap NAS/NAE/IOM, to what degree should the Academy attempt to speak with one voice?
4. In the decades ahead should the mix of advisory bodies now being called upon by the government, in which the academies play a prominent but not exclusive role, be adjusted in the light of present experience and/or future needs?
5. Is the Congressional Charter for the Science Academy, in its present form, fully adequate to meet the needs of the academies and the government in the coming decades? Should the academies, other than the Science Academy, be defined and recognized by the government and the Congress by incorporation into the present charter or through separate charters, or is the present arrangement with respect to charters satisfactory?



6. Is the project-study approach, which now predominates in defining, funding, performing, and reporting academy studies, the optimum approach, or are there other mechanisms which for some purposes are better suited to the capabilities of the academies and the needs of the government?
7. Should the government take any steps over the longer term to strengthen and augment the ability of the academies to initiate their own studies on topics for which requests have not been made by agencies of the government, including steps that would make such studies financially feasible?
8. To what extent does, or should, the Academy incorporate policy concerns into their scientific and technical recommendations and reports, i.e., should policy influence Academy recommendations or should the recommendations be guidelines for policymakers?
9. How well do the academies' policy committees, such as the Committee on Science, Engineering and Public Policy (COSEPUP), the Government University-Industry Research Roundtable, and the Board on Health Science Policy function in providing balanced, relevant, and timely advice?
10. What have been the effects of the series of disciplinary studies covering individual fields of science such as physics, chemistry, and astronomy, and should they be continued? If so, how can they be improved so as to be of maximum benefit to their intended audience?
11. Are there additional functions in the national interest related to science and technology which the academies may wish to carry out and the government would find desirable and support?
12. What is the perception of the academies and their role vis-a-vis the citizens of the country and to what extent should that factor play a role in the government's use and support of the academies?

Other questions may be appropriate to this examination and should also be raised at the hearing. The Task Force recognizes that the academies have long played a significant role in American science policy. The members of the academies, its leadership, and the many scientists, engineers and medical doctors who generously give their time to the work of the academies constitute a unique national asset. As we enter into the post-Gramm/Rudman period in the early nineties and look toward the year 2000 and beyond, what should characterize the interface between the Federal Government and the national academies?

Talking Points

"The Future of the Academies"

James B. Wyngaarden, M.D.

Prepared for the Task Force on Science Policy

House Committee on Science and Technology

May 6, 1986

While I am prepared to provide my views as the Director of a Federal agency that utilizes the services provided by the National Academy of Sciences (NAS) and the Institute of Medicine (IOM), I feel obliged to acknowledge that I am a member of the NAS and the IOM and have and do occasionally serve as a member of various NAS and IOM committees. The committees I have worked with deliberate policy issues on the life sciences, research manpower development, and Government-university-industry relations. While I am clearly a participant, I will strive to be objective in my views.

[Response to Question 1:]

o The academies do fulfill the original mandate and respond when called upon by the National Institutes of Health (NIH) to "investigate and examine . . . any subject of science. . . ."

o The charter also allows for experiments and reports.

--To my knowledge, we have not called upon them to conduct any "experiment"; however, within the past two years the NAS declined to undertake an investigation because the agencies involved requested that the study include the acquisition of new information. (Five agencies requested that the Academy conduct a study of the Nation's scientific research facilities, basing their investigation on factual information about the status of those facilities.)

--In one recent experience, a requested "report" was not forthcoming because the study group did not achieve a scientific consensus on a subject related to nutrition. This will occasionally be the result when objective individuals must subjectively interpret incomplete information.

[Response to Question 2:]

o Because policy issues are becoming increasingly complex, the development of useful and productive recommendations may in the future sometimes require a more collaborative mode of operation than the one that now exists between the Academy and sponsoring agencies. Currently, once a project is begun, an agency's role is quite limited. A more collaborative mode might well allow for broader and deeper consideration of all aspects of some problems. Occasions for this kind of departure from the usual, fully independent mode of operation would, of course, have to be selected very carefully.

o In a few instances we have sought scientific advice (e.g., radio-epidemiologic tables, nutritional RDA), but, being an agency of science ourselves, our need is usually for policy recommendations that affect science (e.g., examination of issues surrounding the use of animals in research), or that provide centralized data bases on science (e.g., the Doctorate Records File). Some of the Academy projects are initiated by us (e.g., the 1984 study of the NIH organizational structure) and some are mandated by Congress (e.g., the continuing study of national needs for biomedical and behavioral research personnel).



o The advice provided by the academies usually meets our needs and the information compiled and reported frequently reaches a much wider audience. As with any organization, there is variability in effectiveness and in the manner in which projects are planned and carried out. A centralized Academy report review process smoothes the content of issued reports into a fairly uniform quality. Some Academy studies actively seek the advice of our expert staff, yet all projects have maintained sufficient independence to avoid possible charges of collusion, perhaps even to an excessive degree.

o Academy advice does not come cheaply, and I expect that during an era of fiscal constraint, economies may not permit us to seek Academy advice as frequently as in the recent past.

[Response to Question 3:]

o Speaking in a single voice for science may constitute an ideal that is not always attainable. A more realistic aim for the academies may be the maintenance of harmony among its several voices. From time to time there may develop fundamental differences in the interpretation of available scientific information or in judgment about how limitations of available information should be treated. While it is essential that society be spared the confusion of openly conflicting views, it is equally important that what is known about scientific information and its limitations be made available. For the most part, the Academy has met this type of responsibility effectively.

[Response to Question 4:]

o I have already suggested that the increasing complexity of some scientific and social issues may require a different mode of operation than is now typical of the academies. Increased flexibility in Academy operations is one alternative to the development of a different mix of advising bodies. That some adjustment will be necessary in the decades ahead is probably as inevitable as the advancement of science and the increased complexity of the issues that confront us.

o Competition in animal systems tends to strengthen and improve their viability. In providing scientific advice, the Academy has an ecological niche of its own. The Academy chooses not to compete with commercial providers of policy and management studies. In providing science policy studies, overviews and forecasts for science fields, and science management guidance, the Office of Technology Assessment (OTA), Congressional Budget Office (CBO), and Office of Science Technology Policy (OSTP) have been providing some impressive, timely, and balanced analyses, as has the Academy. There is need for all of these and for the special commissions such as the one following up the Three Mile Island accident. We are pleased to have direct access to the capabilities of the Academy. In addition, there have been occasions when we might have liked that the Academy submit a competitive proposal in response to a general request for proposals. But, even justifiably non-competitive studies could benefit from responsible competitive-style proposals showing more forethought about what will be accomplished and how.

[No response to Question 5. Optional response is appended.]

[Response to Question 6:]

o From an organizational standpoint, the project-study approach has, to date, met our needs quite well. This approach may have higher associated start-up costs, but it allows for the selection and assignment of the best suited individuals to guide studies of current issues. In some cases standing committees mandated to provide continuing advice seem to be less successful. When standing committees are deemed necessary, they should be set up to operate on a precisely designated rotating membership basis (many standing committees already have such a policy).

[Response to Question 7:]

o You asked me to consider whether the Government should take steps financially that would enable the Academy to initiate its own studies. The extent to which financial insecurity may discourage the most able potential staff from accepting Academy employment is a consideration. Greater financial security might well enable the Academy to be more successful in competing for the best available talent to staff its activities.

211

o In times of fiscal constraint, however, it may not be appropriate for Government agencies such as the NIH to offer long-term support for the Academy to initiate its own studies. The Academy offers advice to Federal and other sponsors with specific needs. It would be more appropriate for Federal agencies to have the funds to use judiciously to support studies of pragmatic significance.

[Response to question 8:]

o The Academy should be fully familiar with, but not bound by, the policy concerns of sponsoring agencies. Policy recommendations made by the Academy would then be more likely to have practical utility. The Academy should continue to be an independent body, and Federal policy makers should heed but not be bound to Academy recommendations.

o We have noticed that, on occasion, the absence of adequate consideration of policy concerns has produced less than optimal results (NIH organizational study). An issue that is essentially scientific in nature may require that related policy issues be recognized and dealt with openly and fully (e.g., the nutritional requirements issue). On the other hand, policy issues must never be allowed to obscure scientific evidence.



[Response to Question 9:]

o Over the long term policy committees such as the Committee on Science Engineering and Public Policy (COSEPUP), Government-University-Industry-Research Roundtable and the Board on Health Science Policy have served an important purpose in providing a forum for the development of sound policy. By avoiding involvement in making recommendations and in the acquisition of new information however, these committees limit the scope and utility of their advice. Attention to the issue of recognizing a need and then directing the acquisition of factual information would increase the value of their deliberations.

[Response to Question 10:]

- o The recent "Pimentel Report" on chemistry called attention to the prominent role this discipline is playing in the health sciences. It revealed, for example, that some 22 percent of university chemistry department research is funded by the NIH. It also offered reasons why the average NIH grant should be larger. This study also provided useful information about the status of chemistry research instrumentation at a time when our instrument support policies are under review.
- o I hope that a current study of "Research Opportunities in Biology," now just getting under way, will be equally useful.

[Response to Question 11:]

- o You asked about possible new general functions for the Academy. I can think of special studies but have no new general functions to suggest.

[Response to Question 12:]

- o Much of the citizenry views the Academy as a kind of "Supreme Court" of the sciences, remote, highly respected, and trusted. These circumstances encourage Government use of Academy capabilities. They also militate strongly against the dilution of Academy committees by the appointment of lay members for socio-political purposes. A broader base of support might permit a more detached perspective to guide the consideration of questions that should be addressed.
- o Interface between Government and the academies should be characterized by mutual respect and collegial effort to solve national problems of science <sup>^</sup>policy.
- o The academies must remain free to criticize Government policy and programs, else they cannot serve the national interest. At the same time, they must be held to an extremely high standard of performance--again, in the national interest.

o We should remember that scientists are citizens too, and allow their civic responsibilities to influence their recommendation on focused issues. I think Academy reports demonstrate an awareness and respect for the concerns of the American public as well as the needs of American science.

[If pressed for a response to Question 5, consider the following:]

o Whether the existing arrangement with respect to charters is optimal from an administrative standpoint (and I am not prepared to discuss that issue), the existing relationship among the academies is sound and effective. It might be difficult to maintain the harmony we have espoused if separate charters were established. Furthermore, the National Research Council (NRC), which should serve all the Academies, applies methods from all branches of science, and seeks counsel from the NAS, IOM, or National Academy of Engineering membership, as needed. This current arrangement appears to work quite well. Separate charters would probably increase costs and decrease effectiveness of the kinds of services supplied by the NRC.

## A LOOK TOWARD THE FUTURE OF THE HEALTH SCIENCES\*

by

James B. Wyngaarden, M.D.\*\*

It is an honor, indeed, to be asked to address this gathering of representative leaders of many of our Nation's major scientific organizations. I will confess it to be a bit overwhelming to realize that the membership of your 28 constituent societies totals more than half a million scientists. Although we come from many different disciplinary backgrounds, we have common interests with respect to our roles in society, the issues involving science, and government. We are also seeing a trend toward convergence within science itself. Certainly in my area of special interest, biomedical research, there has been a continuous process of blurring of disciplinary lines and of expansion into areas that only a few years ago were considered to be outside our scope of interest and inquiry.

I will take this opportunity to tell you some things about the National Institutes of Health and in doing so will trace developments in medically related sciences and in the activities of our agency as a stimulus and source of support for American biomedical research. In the course of my remarks I will venture some cautious looks toward the future of the health sciences. Before doing so, however, I wish to comment briefly on a special period in the past.

In biology, in chemistry and in physics the 1880s were a time of rapid advancement and discovery. It is interesting to note how many scientific institutions are observing their 100th anniversary in this decade. The National Institutes of Health is one of them. In 1987 we will be celebrating "A Century of Science For Health."

---

\*Address given at the Semi-Annual Meeting of the Council of Scientific Society Presidents, Washington, D.C., May 14, 1986.

\*\*Director, National Institutes of Health, Bethesda, Maryland



The NIH came into being at a time when medical science in the United States lagged far behind the state of knowledge in Europe. Studies in the new discipline bacteriology, led by Robert Koch and Louis Pasteur, were taking place in more and more European laboratories but few Americans had participated in those advances. A yellow fever epidemic in 1878 had created widespread alarm in the United States and a variety of measures were proposed for its prevention and control--none particularly effective. Other communicable diseases, such as cholera and tuberculosis, were also matters of serious concern and because travelers and immigrants were thought to be bringing the diseases into the country, efforts to arrest this spread of contagion were concentrated at ports of entry. Thus, in 1887 a one-room laboratory was set aside in the Marine Hospital on Staten Island in the Port of New York, and it was dedicated to research on communicable diseases. Called the National Laboratory of Hygiene, this modest facility ultimately became the National Institutes of Health. The laboratory was a fragile transplant from the fertile fields of the European medical science.

Soon after establishing the hygienic laboratory, its director, Dr. Joseph J. Kinyoun, arranged for a six-month assignment to two of the most famous medical laboratories in Europe, that of Dr. Robert Koch in Berlin and the laboratory founded by Louis Pasteur in Paris.

The European roots of the NIH are fresh in my mind, inasmuch as only three weeks ago I participated in a centenary celebration of the founding of Heidelberg University. Rather than celebrating the events of a single century, however, Heidelberg was observing its 600th anniversary. I was impressed, indeed, to recall that the university was more than a hundred years old when Columbus began making his voyages of discovery. Although I mentioned the NIH centennial when speaking at the Heidelberg observance, you can be sure I did it with a certain humility.

For the first 50 years of its history, the National Institutes of Health was essentially an independent, free-standing laboratory of limited size. It was moved to Washington before the turn of the century and in 1930 was renamed the "National Institute of Health."

The modern era of the NIH, as well as that of biomedical research in our country, began when the government and non-government research laboratories, mostly in academic institutions, joined their efforts in carrying out research during World War II. To meet the urgent need for additional knowledge on how to deal with the health problems of the armed services, the Government turned to the established, non-Federal laboratories for help in conducting vital research. Grants and contracts were awarded for the support of such essential investigations. The arrangement worked exceedingly well. The newly-formed partnerships greatly accelerated progress in research and development across the spectrum, from the most basic research to studies on the widespread application of newly formulated measures for prevention, diagnosis, and treatment of disease.

By the end of the war, the U.S. Office of Scientific Research and Development was administering a large number of medically-related research projects. A leading American scientist, Dr. Vannevar Bush, the President's Science Advisor, urged that the Government continue to support in peacetime the medical research then underway in many universities and hospitals. After Dr. Bush's proposal was accepted, the National Institute of Health was given the responsibility to administer the ongoing projects. This peacetime collaborative effort represented a significant change in national policy--it was a frank recognition of the mutual benefits to be realized from such a partnership.

Dr. Bush's formal recommendations were made in a report written in 1945, titled "Science--The Endless Frontier." He asserted that, "The publicly and privately supported colleges, universities, and research institutes are centers of basic research. They are wellsprings of knowledge and understanding. As long as they are vigorous and healthy and their scientists are free to pursue the truth, wherever it may lead, there will be a flow of new scientific knowledge."<sup>1</sup>

Dr. Bush was careful, however, to emphasize that in the course of supporting research and training, the Federal Government should not interfere with the freedom and integrity of academic institutions. Specifically, he recommended that government grants should allow complete

independence and freedom for the scientists to determine the nature, scope, and methodology of his or her investigations. "Scientific progress," he said, "results from the free play of free intellects working on subjects of their own choice in the manner dictated by their curiosity for exploration of the unknown."<sup>2</sup> It is on this philosophical foundation that the research support programs of the National Institutes of Health were established and continue to flourish.

Our commitment to fundamental research has been sustained over the years, in fact it has grown stronger. In 1970 it was estimated that 30 to 35 percent of our budget was for basic research. By 1980 basic research was 52 percent. In 1986 it was increased to 63 percent. This rapid increase is partly due to the priority we have given to investigator-initiated grants and a marked decline in the use of contracts. It also reflects the accelerated pace of discovery in molecular biology, genetics, and other exciting areas where each new finding generates a family of new questions.

The key instrument that NIH has used to provide support for biomedical research is the Project Grant, each made to fund an investigator-initiated project proposed to the NIH by an individual scientist. In 1986 more than 57 percent of the total NIH budget of over \$5 billion is devoted to such Project Grants. We believe that they foster creativity and excellence and are an effective instrument for involving our country's finest scientists in the national effort to improve health through the advancement of knowledge.

In the short period of five years from 1940 and 1945, the NIH changed from a small Federal laboratory, whose activities were almost entirely in-house, to an agency whose focus turned increasingly to the support of research in non-Federal institutions. Addition of the extramural dimension to the NIH was accompanied by increases in budget--increases that have been spectacular. In terms of purchasing power in constant dollars, the total budget of NIH grew from 1945 to 1968 at an astounding average rate of 24 percent per year. The growth per year since '68, taking inflation into account, has been much less--about 2 percent per year. (Slides 1a, 1b, 1c)



The extremely rapid growth of the budget in the earlier period resulted in part from expansion of the scope of the agency through the creation one-by-one of new institutes. There are now 12 institutes, most of them oriented to specific organ systems or to families of diseases, as for example, the National Heart, Lung, and Blood Institute, the National Eye Institute, the National Cancer Institute, and the National Institute of Allergy and Infectious Diseases.

It was inevitable that the steep climb in the NIH budget must taper off and it began to do so in the mid 1960s. To forestall or at least to ameliorate this change, dedicated proponents of biomedical research took the offensive first under the banner of initiatives against the killers--heart disease, stroke, and a few years later of a war against cancer. For a time the Democratic Congress and the Republican Administration attempted to outbid each other in terms of appropriation and organizational innovations to hasten the conquest of cancer. Subsequently, proponents of research on heart disease also have been successful in attracting special attention and funds for research with this number one killer.

Between 1971 and 1973 the budget of the National Cancer Institute more than doubled in current dollars. It tripled by 1975. The National Heart, Lung, and Blood Institute also experienced a period of rapid growth, increasing by 35 percent between 1971 and 1973, and doubling by 1977. The budgets of both these institutes grew faster than the total NIH budget during the early '70s, and consequently most other components had reductions in their purchasing power for 5-7 years, thus without much growth for NIH as a whole. There was a remarkable revision of national priorities toward cancer, heart disease, and to a lesser extent, stroke. By the late '70s, however, the growth differentials between institutes had largely evened out.

For the period beginning in 1972 and continuing to the present, another set of budget adjustments has taken place. The salient feature of these adjustments was the marked shift in the allocation of funds to favor the support of Research Project Grants. In the period from 1972 to 1984 the budget for Research Project Grants increased from 44 to 66 percent of



the extramural budget. There was a concomitant reduction in the budget for contracts and training. The total number of such Project Grants being supported during 1972 was 10,290, and by 1985 the number had grown to 18,219. Throughout this time the average award per project remained virtually unchanged in constant dollars. However, indirect costs took an increasing share of the research award, rising from 21 percent in 1972 to over 31 percent in 1985. Consequently, the real dollars available per project for direct costs were reduced. (Slides 2, 3 and 4)

Another pressure has developed, not directly the result of the budget crunch but an effect of the progress of science. The number of excellent applications for grants increased at a much more rapid rate than our ability to fund them. The number of competing applications for Project Grants reviewed in 1985 was 18,674, more than double the number reviewed in 1972. (Slide 5)

In the past decade we have become increasingly concerned about maintaining a relatively stable and predictable level of new and competing renewal Project Grants. The number of competing awards has fluctuated greatly since 1972, ranging from a total of 2,592 in FY 73 to a high of 6,246 in 1985. Such fluctuations not only create financial problems for grantee institutions but adversely influence the career decisions of graduate students as well as young scientists. (Slide 6)

We have recognized that to assure future health gains, the current national research capability must be sustained and enhanced. As applied to Research Project Grants, a major goal has been to minimize year-to-year fluctuations of funds available for the new and competing renewal awards. Historically, the average grant award has been made for a period of from three to four years, and a grant may be renewed if the renewal proposal is successful in competition with other renewal applications as well as new proposals. Thus, the amount of funds available for new and competing renewal awards is an index of opportunity from the viewpoint of the investigator. Our effort to maintain an adequate and predictable level of funding for new and competing renewal awards has been called in government jargon the "stabilization initiative."

The stabilization initiative has been an important element of the NIH budget for the past seven years. I will not go into further detail regarding it, other than to say that its purpose is not only to undergird the investigator-initiated Project Grant as the prime means for supporting research but also to reassure young investigators by demonstrating to them that even in a time of budget constraints research careers are not restricted to the very few. In recent years, the priority of research grants has resulted in less funding of centers, training, and clinical trials.

However, in spite of the progressive annual shift of funds into Research Project Grants, the number of applications has grown even faster than resources. In 1975 we were able to fund about 65 percent of grants eligible for award, but in 1984 and 1985 the award rate was only about 37 percent. (Slide 7)

Although fiscal constraints are responsible for many difficulties I have been discussing, certain attributes of the current extramural award system may be more burdensome than necessary for the investigator, the university, and the NIH peer review system.

In our judgment, one of the factors that is contributing needlessly to the workload of both the grant applicant and the NIH peer review system is the excessive complexity and sheer bulk of the research grant application. We will shortly be proposing page limitations in grant applications. This should reduce reviewing time of study section members as well as preparation time for the applicant.

When the award rate falls the percentage of first-time applicants receiving awards also falls. We believe it is essential to the vitality of the scientific enterprise and to the morale of the field that young scientists be encouraged. We have recently announced a new program called FIRST awards (First Independent Research Since Training), a modification which raises the term of the initial award from 3 to 5 years, and the total to \$350,000 of direct costs for the 5 years. This should obviate the difficulty for young investigators who have often found it necessary to

begin the process of reapplication as early as 18 months after the initial award. It also encourages more creative, less defensive research.

Finally, we have also expanded the number and types of longer-term support for outstanding M.D. scientists through a new program called MERIT awards (Method of Extending Research In Time). This program will involve facilitated extensions of 5-year awards for an additional 3 to 5 years on the basis of a detailed progress report rather than on a formal reapplication.

We believe that a greater number of longer grants to both first-time and established investigators represents an efficient and prudent investment of Federal funds that should lead to increased productivity and creativity. However, the budgetary implications in the fourth and fifth years and beyond are substantial, and in the absence of major funding increases could reduce the number of new and competing renewal grants we would be able to make in future years.

The NIH provides support for research training through a variety of types of grants. Currently more than 10,000 trainees are being supported through our different training programs at academic medical centers, research hospitals, and laboratories throughout the United States.

Additionally, at the site of our headquarters in Bethesda a highly effective training program is conducted in our own laboratories and clinics. A few words regarding these programs are appropriate in the context of training.

About \$600 million, or more than 10 percent of our total budget, will be used this year for research in NIH's own laboratories. About 2,500 scientists with doctoral degrees and as many as 3,500 trained support staff are engaged in our intramural research program. The diversity of the program is remarkable. It consists of all manner of units, some with targeted goals, some with total scholarly freedom, some with clinically oriented concerns, some with interests in basic biology that cover the



gamut of living organisms and the whole range of biologically relevant questions. The intramural programs of NIH have been highly productive.

Research training is an essential and integral part of our intramural activity. We offer a variety of structured experiences for postdoctoral trainees in graduate and professional level programs in the clinical and basic sciences. At this time 886 trainees are participating in our regular programs.

We also conduct the NIH Visiting Programs for talented scientists throughout the world who come to Bethesda to share in the resources of NIH. Through this program, distinguished scientists at all levels of their careers are invited to receive further training or to conduct research in their biomedical specialties. Stipends are provided and each participant in the Visiting Program works closely with a senior NIH investigator who serves as sponsor or supervisor during the visitor's period of award or appointment. Over 1,100 scientists from 70 countries are participating in our Visitors Program. Additionally, about 400 guest workers also participate in research at the NIH. These scientists do not receive stipends but are provided laboratory space and research support.

The flow of young people through the laboratories exerts a powerful influence. The trainees with their imaginative and probing minds provide the kind of challenge to senior scientists that graduate students offer in the university setting and their presence is an essential element in a continuous process of renewal for our staff scientists.

Permit me to turn now to some general comments about the future. Concurrently with, and in large measure as a result of, the development of the government-academic partnership, there has been amassed a spectacular store of biological knowledge. This has made possible tremendous advances directly relevant to human health. We are in an age of molecular biology, an era that was in large part spawned by the government/academic partnership.



The biological revolution is far from over and, in fact, is now approaching major questions with immediate relevance to human health. Key discoveries in molecular biology, genetics, and immunology have led to the widespread use of techniques that are enabling scientists to address fundamental questions about the nature of living organisms.

Cells and bacteria can be transformed into factories to produce custom-made monoclonal antibodies or valuable hormones and growth factors. It is also significant that these discoveries were made possible through applying information and experience gained in one scientific discipline to problems in another. These advances, which were made in the past decade, are still diffusing into existing fields of investigation. Questions that went unanswered for lack of appropriate technology are now under attack. Their solutions will accelerate our progress against disease as well as raise new questions to explore.

I will mention, as examples, a few accomplishments that promise to lead to opportunities for new achievements in diagnosis, treatment, prevention, and understanding of the physiological processes underlying disease states:

#### New Research Emphases

- o One current area of progress and promise is in structural biology. Work on cell membrane and receptor structure and function can lead to design of tailor-made drugs for more effective tailor-made action. Recently, investigators have determined the complete, three-dimensional architecture of the common cold virus using x-ray crystallography employing a high energy synchrotron source. Scientists have long known the general shape of the cold virus, which under the electron microscope shows an outer wall composed of 20 triangles that fit together to form the geometric shape known as an icosahedron. Inside the hollow protein shell is the genetic material which, when released, directs the cell to replicate the virus.

The new studies provide a stereo view of the exact position of the molecules making up the protein structure showing that each triangle

of the protein shell has peaks and valleys formed by the irregular shape of protein molecules making up the shell. The part of the shell that must attach to a cell to cause infection lies within a deep cleft or "canyon" on each of the 20 triangular sides and appears to be too narrow for antibodies to reach. However, this finding raises the possibility that a molecule could be synthesized that would be small enough to enter the canyon and bind to the attachment site, preventing attachment of the virus to the cell and, consequently, preventing infection.

- o Technological advances in areas such as X-ray crystallography and magnetic resonance imaging provide new opportunities to investigate the structural properties of physiologically active molecules. One of the most revealing and rapidly evolving research tools now being used by molecular biologists is magnetic resonance imaging spectroscopy. Using this technique it is possible to determine the chemical composition of biologically important molecules, the length and nature of the bonds holding the atoms of the molecule together, and the three-dimensional arrangement of those atoms. A significant advantage of this technique is that studies can now be performed on molecules in their typical physiologically active state, that is, either within the living organism or in aqueous solution rather than in an unnatural solid state.
- o Important advances in the technique of genetic mapping have been facilitated by the increasing availability of DNA probes. To foster genetic research, the NIH recently established a repository in which DNA segments will be collected, stored, and distributed to scientists around the world. The repository will eventually store copies of most of the 100,000 human genes and will enable scientists to locate and acquire easily the specific pieces of human DNA they need to locate genes on specific chromosomes, to distinguish normal from abnormal genes, to insert genes into chromosomes, and eventually to treat genetic diseases.

Recent successes in this field include the discovery of genetic markers for cystic fibrosis and Huntington's disease. This research and related work opens up the possibility of isolating the gene and the gene product. Then the nature of the genetic deficit would become apparent, permitting the development of more rational treatment or prevention strategies.

Although the marker for cystic fibrosis is diagnostic for most carriers of the disease in families with a history of the disease, it is not specific enough to diagnose asymptomatic carriers in the general population. Such a test requires isolation of the CF gene itself, a task now technically feasible because of the new findings.

The marker that is associated with the Huntington's disease gene was found on a particular chromosome (Chromosome 4). For a test to be reliable, scientists must confirm that this location applies to all HD families. So far, 15 extended families have been analyzed and all carry the marker on Chromosome 4. An NIH grantee at the Massachusetts General Hospital plans to confirm this location in 25 families before they use this marker to test people at risk. The test for HD so far has been about 95 percent accurate. Identification of a second marker on the other side of the gene, a so-called "flanking marker," would make the test 99.8 percent accurate. The flanking marker would also hasten progress in locating the gene itself.

#### New Products

- o Recombinant DNA technology has recently been successfully applied to the synthetic production of blood coagulation factor VIII, which is absent in people who suffer from hemophilia A, and which must be replaced to control this bleeding disorder. This achievement marks the cloning of the largest, most complex protein produced through genetic engineering. Although it may require several years to develop and test this product clinically, the achievement of a laboratory-produced clotting factor is of great importance because it should lead to a less hazardous and a less costly alternative to plasma derived factor VIII.



- o Basic studies in immunology have led to the development of important techniques that are used in all aspects of biomedical research. Foremost among these techniques is the ability to fuse two cell types, one an antibody producing cell, the other a myeloma (cancer) cell which may be kept alive indefinitely in cell culture. The resulting hybridoma will manufacture highly specific antibody for any number of uses.

Their utility has been extended well beyond basic research and is being extensively applied by the U.S. biotechnology industry. The impact of monoclonal antibody technology is especially strong in the area of in vitro diagnostic products, for example: those to detect pregnancy and ovulation, to diagnose infectious diseases such as strep throat and hepatitis B, to identify pregnant women with the potentially dangerous Rh antigen, to identify biochemical tissue markers for organ transplant procedures, and to detect tumor markers in blood and other specimens from cancer patients. The FDA has already approved more than 150 diagnostic kits that use monoclonal antibodies, most of which are expected to produce results much faster than microbiology-based tests.

Other monoclonals under development are aimed at diagnosis of disease in vivo. Using monoclonals for direct treatment lies further in the future. Some day cancer patients may be administered unmodified monoclonal antibodies or monoclonal antibodies bearing toxin molecules. Such molecular conjugates would be designed so that the monoclonal portion specifically recognizes a malignant cell and the toxin portion, once inside the cell, destroys it. The theory has practical problems and the use of this technique must await further work.

Similar application of monoclonal antibodies in heart disease already seems promising. Experiments in animals have shown that streptokinase-- or another lytic agent--plus a monoclonal antibody specific to cross-linked fibrin can dissolve thrombi in the femoral arteries with fewer systemic effects than are found with other therapies. Injected intravenously, the drug is guided by the antibody to the exact area containing the clot and the streptokinase works as always by



dissolving the clot. Following human studies the system may be useful in myocardial infarction patients, and in those with stroke, pulmonary embolism and deep vein thrombosis.

#### Neuroscience, Endocrinology, and AIDS

- o Investigators in the field of neurobiology have recently succeeded in identifying the locations of several of the more than 30,000 genes that control protein production, and have also produced important new evidence regarding the functions of some of these proteins in the transfer of information within the human brain. These findings are of vital importance to studies of both brain function and neurological diseases.
- o The development of powerful recombinant DNA methods coupled with other recent advances in molecular biology have resulted in a vast accumulation of knowledge about hormones. Prior to the application of these techniques, isolation of hormones involved laborious extraction and purification from large amounts of tissue. New recombinant DNA techniques have already made possible the synthesis of potentially unlimited amounts of growth hormone, somatostatin and clinically active insulin. Recombinant produced insulin is now used for 50-60 percent of newly diagnosed patients with diabetes.
- o Although there is still much to be learned about the biology and pathogenesis of AIDS and accompanying opportunistic infections, the rapid progress that has been made thus far in AIDS research is due in large part to the science base already developed through prior support of viral and immunologic basic research.

This striking array of achievements and perceived opportunities is almost entirely the product of knowledge and understanding acquired in the past 30 to 40 years, and much of it is the product of research during the past decade. Biomedical research is moving forward at an unprecedented pace, and from it have come ever more powerful tools to combat disease and disability.

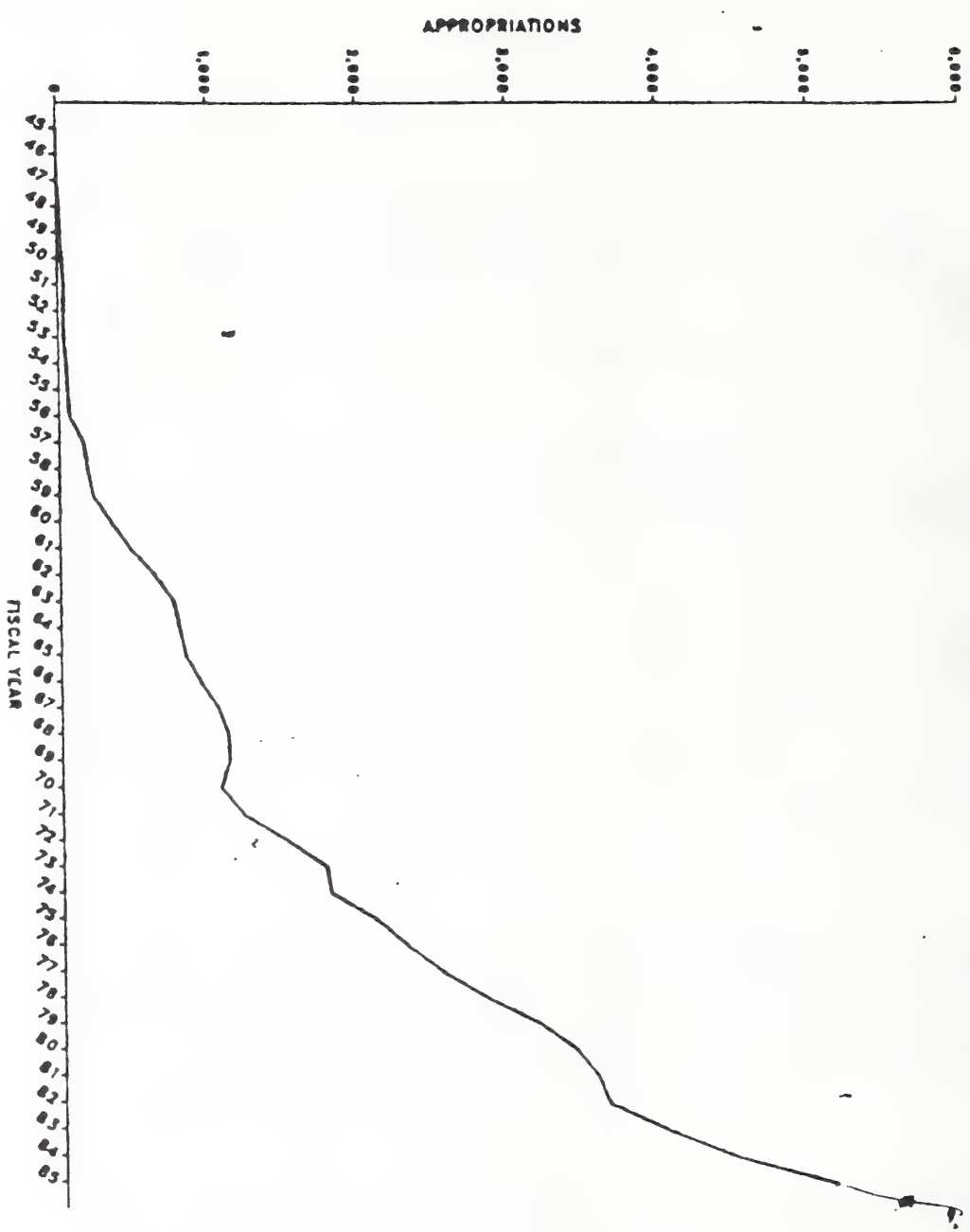
I will be glad to respond to any questions you may have.

REFERENCES

<sup>1</sup>Bush, Vannevar, Science--The Endless Frontier, report to the President on a program for postwar scientific research, 1945, p. 7.

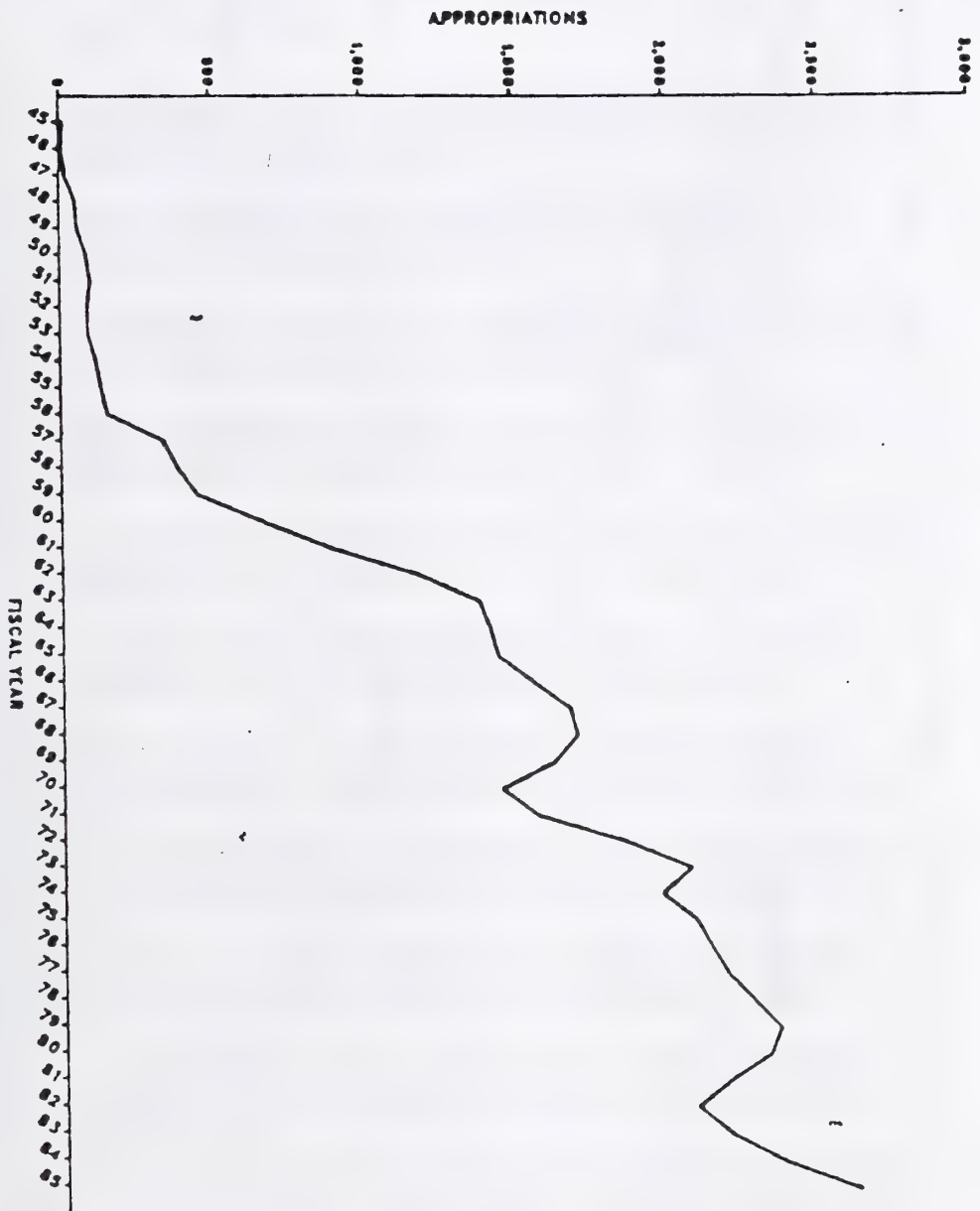
<sup>2</sup>Bush, Vannevar, Science--The Endless Frontier, report to the President on a program for postwar scientific research, 1945, p. 7

# Total NIH Appropriations in Current Dollars, FY 1945-85 Excluding Programs Transferred Out (Dollars in Millions)



NOTES: TQ excluded. 1985 data preliminary.

Total NIH Appropriations in Constant (1975) Dollars, FY 1945-85  
Excluding Programs Transferred Out  
(Dollars in Millions)

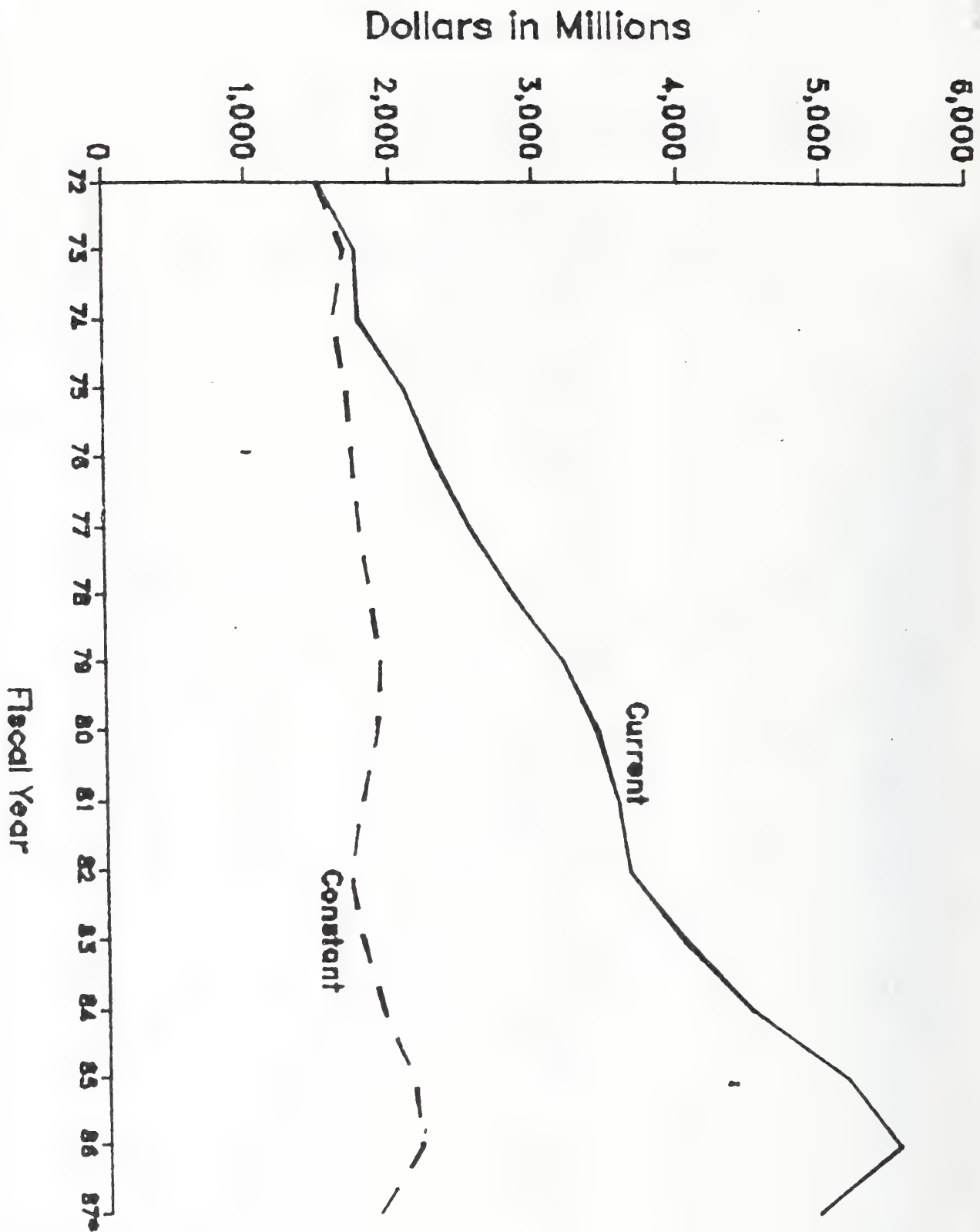


NOTES: Constant dollar conversion uses BRDPI. TQ excluded. 1985 data preliminary.

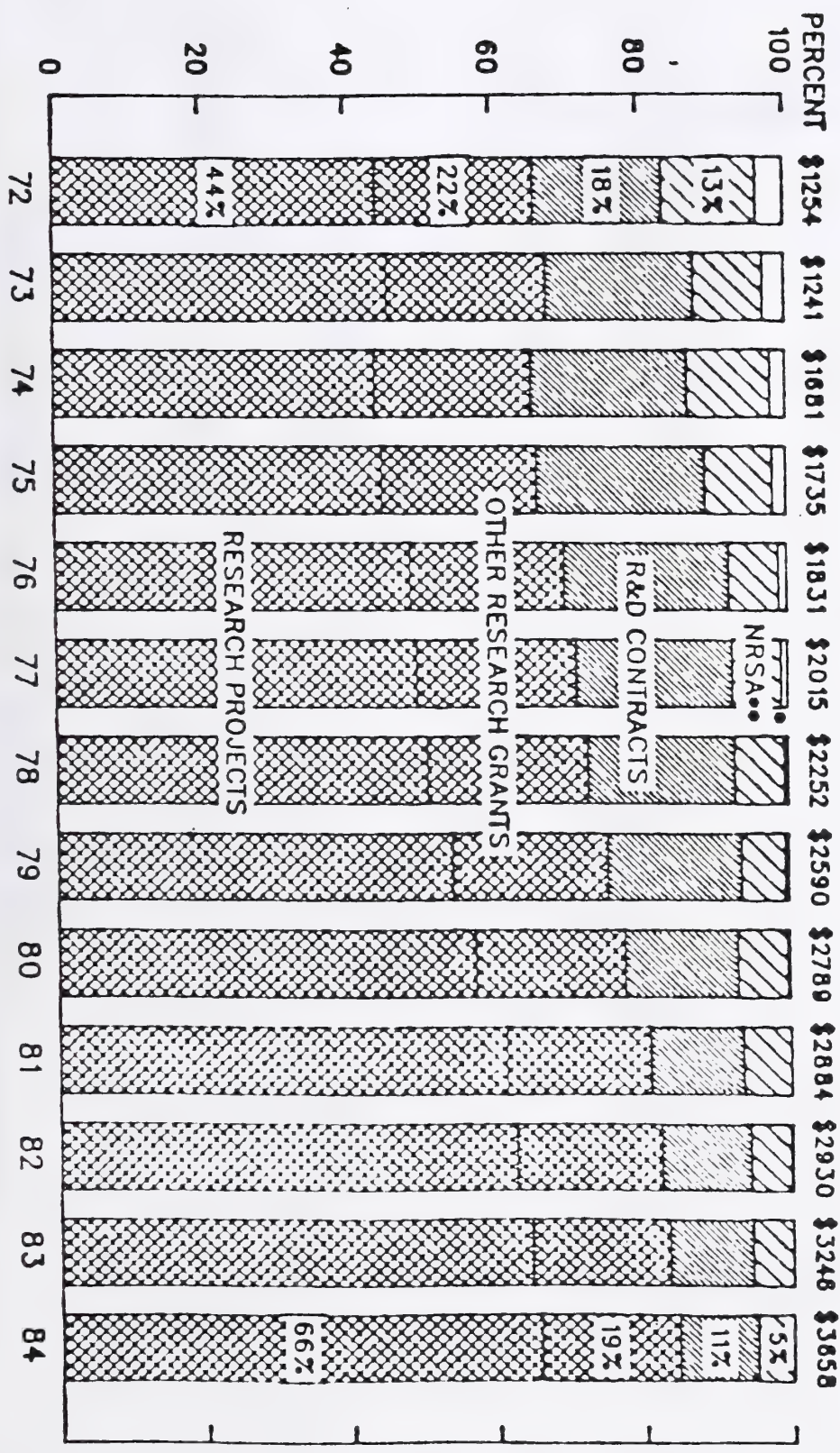
PAB/DPA/OPPE/00, April 1985



(1972=100)



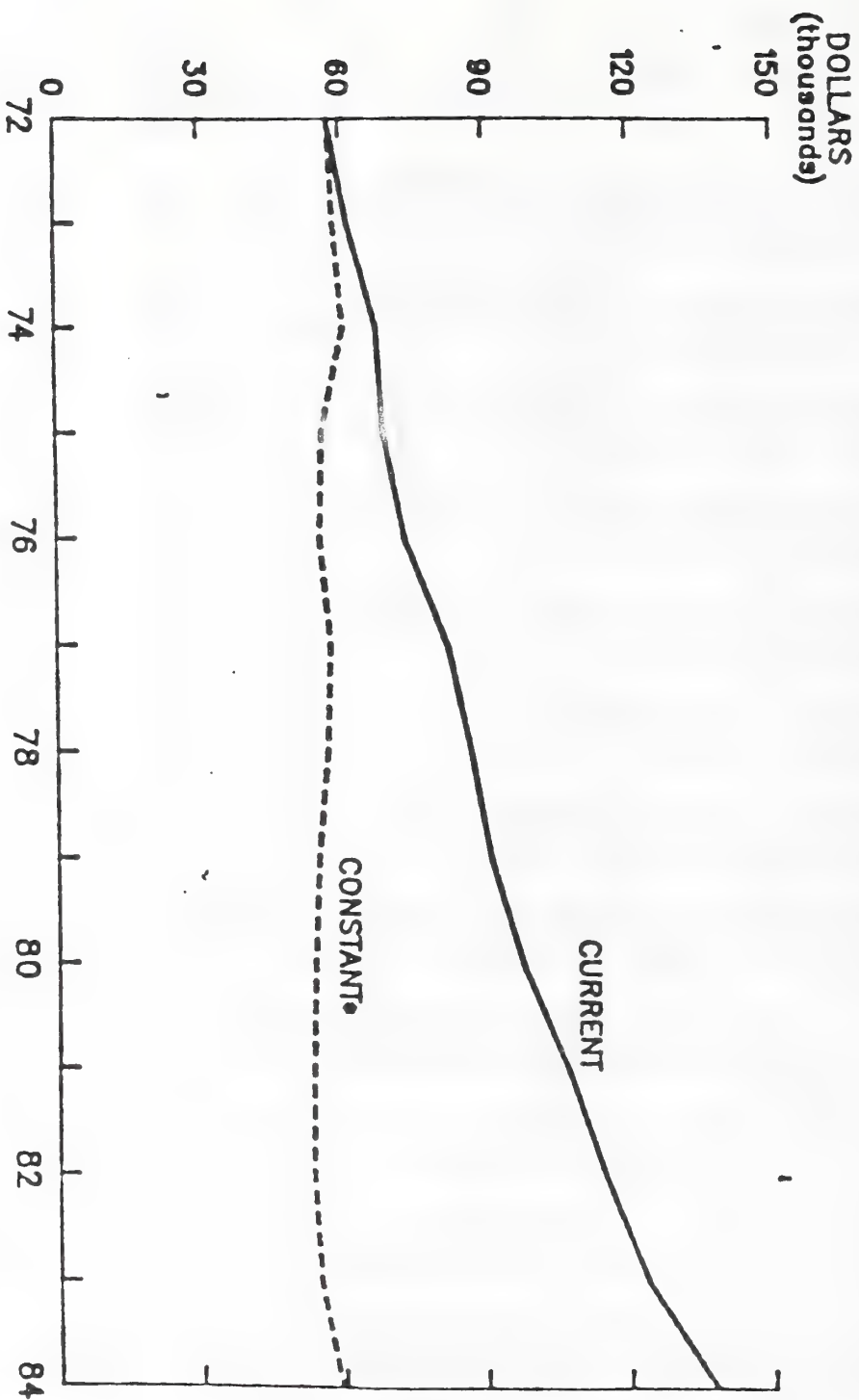
# ALLOCATION OF NIH EXTRAMURAL AWARDS BY ACTIVITY, FISCAL YEARS 1972-1984 PERCENT OF AMOUNT AWARDED (CURRENT DOLLARS IN MILLIONS)



NOTE: EXCLUDES TO. INCLUDES CONSTRUCTION AND MEDICAL LIBRARY GRANTS. INCLUDES PRE-NRSA TRAINING.

SOURCE: NIH, DOD, STATISTICS AND ANALYSIS BRANCH

# AVERAGE DOLLARS FOR NIH RESEARCH PROJECT GRANTS FISCAL YEARS 1972-1984

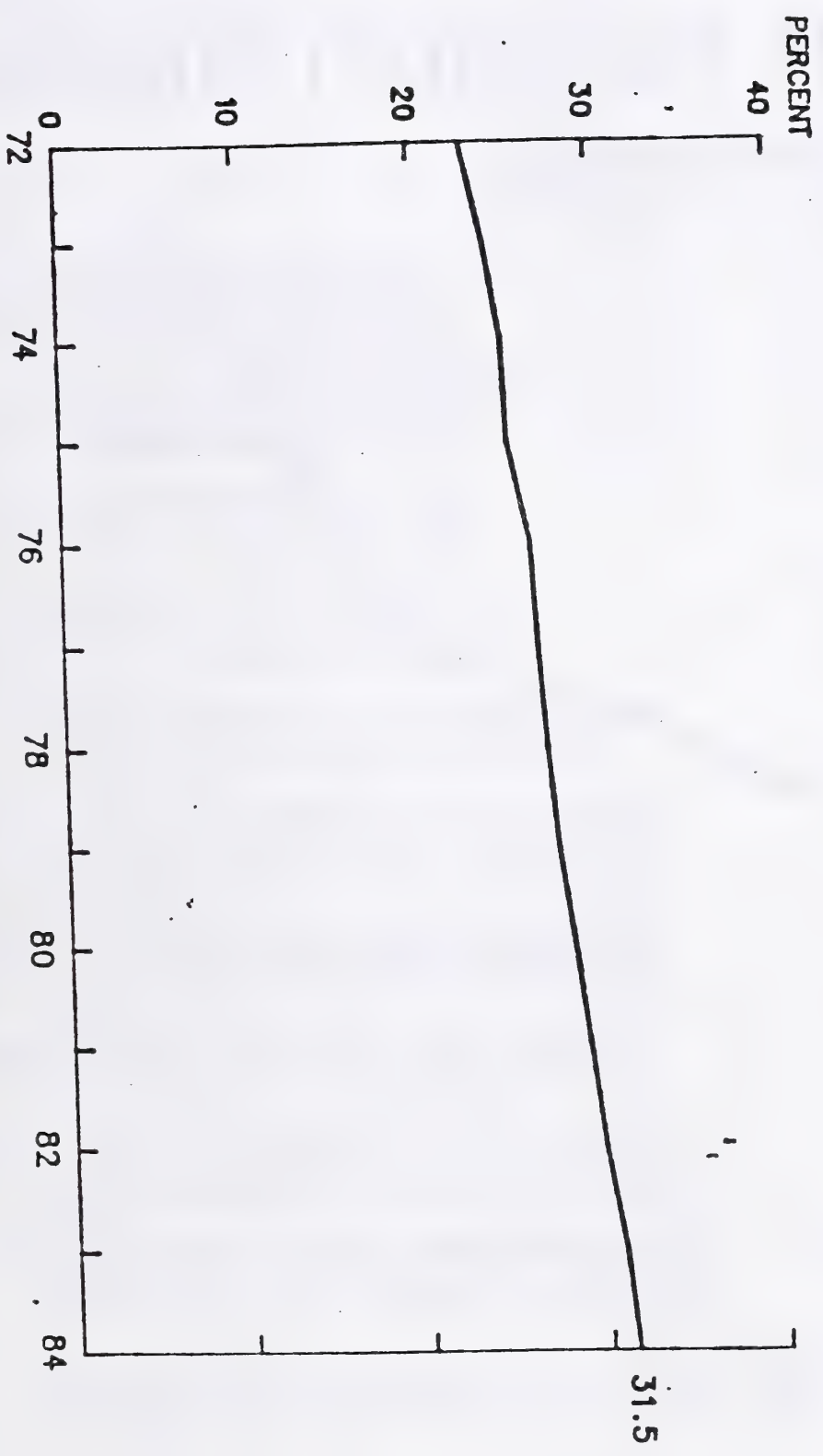


BASED ON BIOLOGICAL AND PHYSICAL SCIENCES  
SOURCE: NIH, DRO, STATISTICS AND ANALYSIS BRANCH

END  
6/10/88

INDIRECT COST PROPORTION OF TOTAL COST\* FOR NIH RESEARCH GRANTS  
FISCAL YEARS 1972-1984

4.



NOTE: EXCLUDES DATA FOR FISCAL YEARS 1972-1984  
SOURCE: NIH, DHE, STATISTICS AND ANALYSIS BRANCH

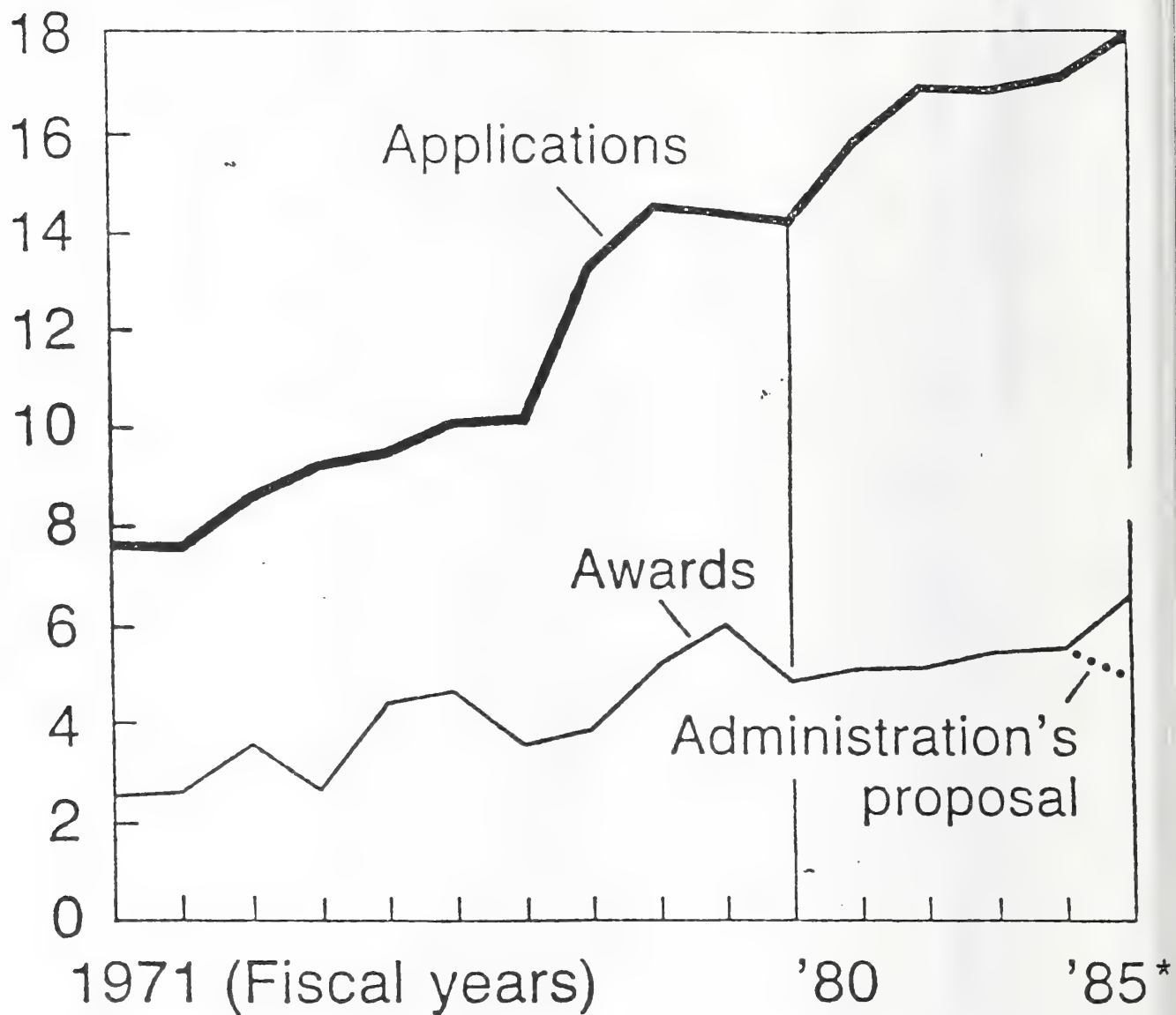
TS4  
v/ues



5

212

# NIH Research Grants (Thousands)

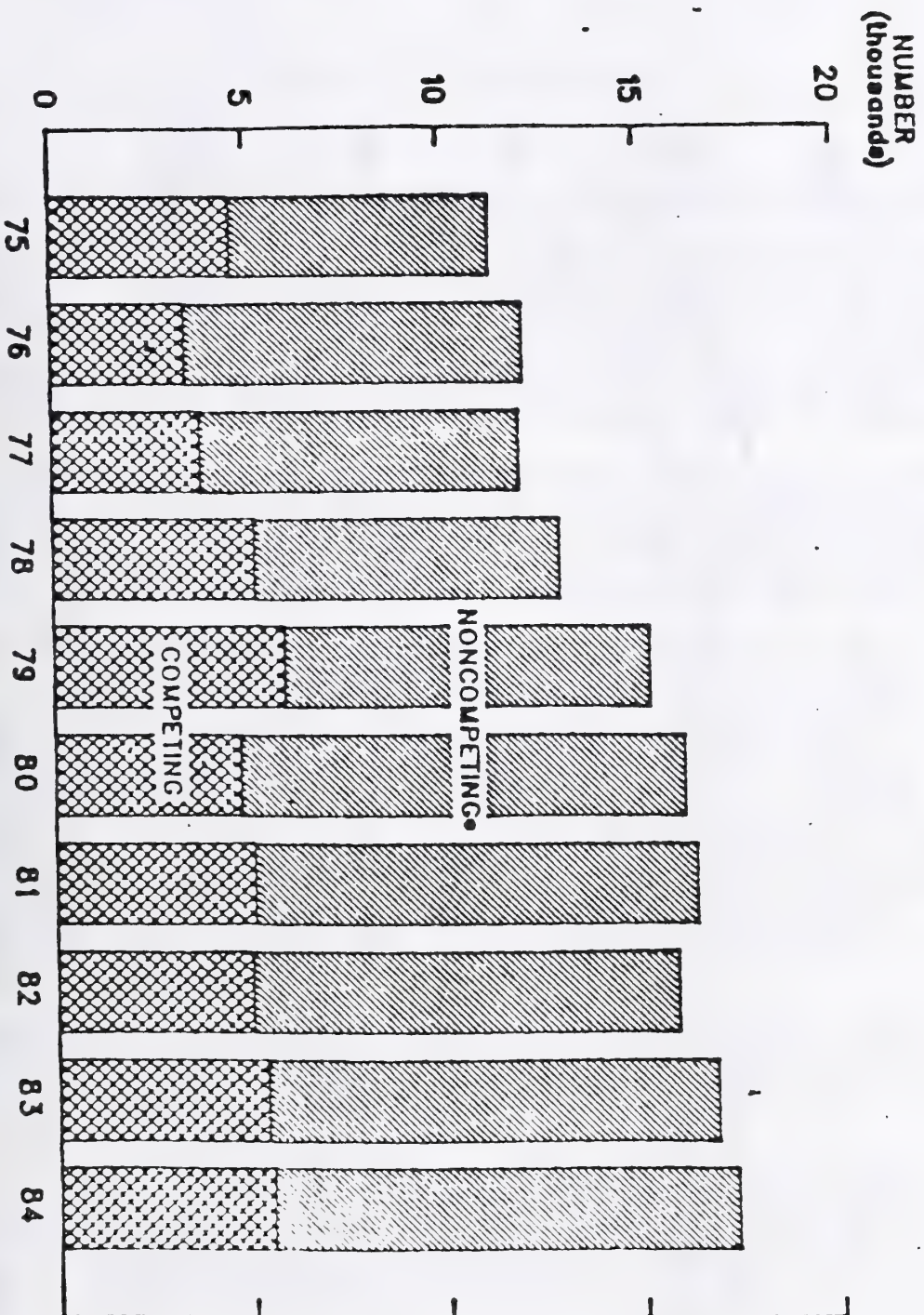


\* Projected

Source: National Institutes of Health

5

NIH RESEARCH PROJECT AWARDS  
FISCAL YEARS 1975-1984



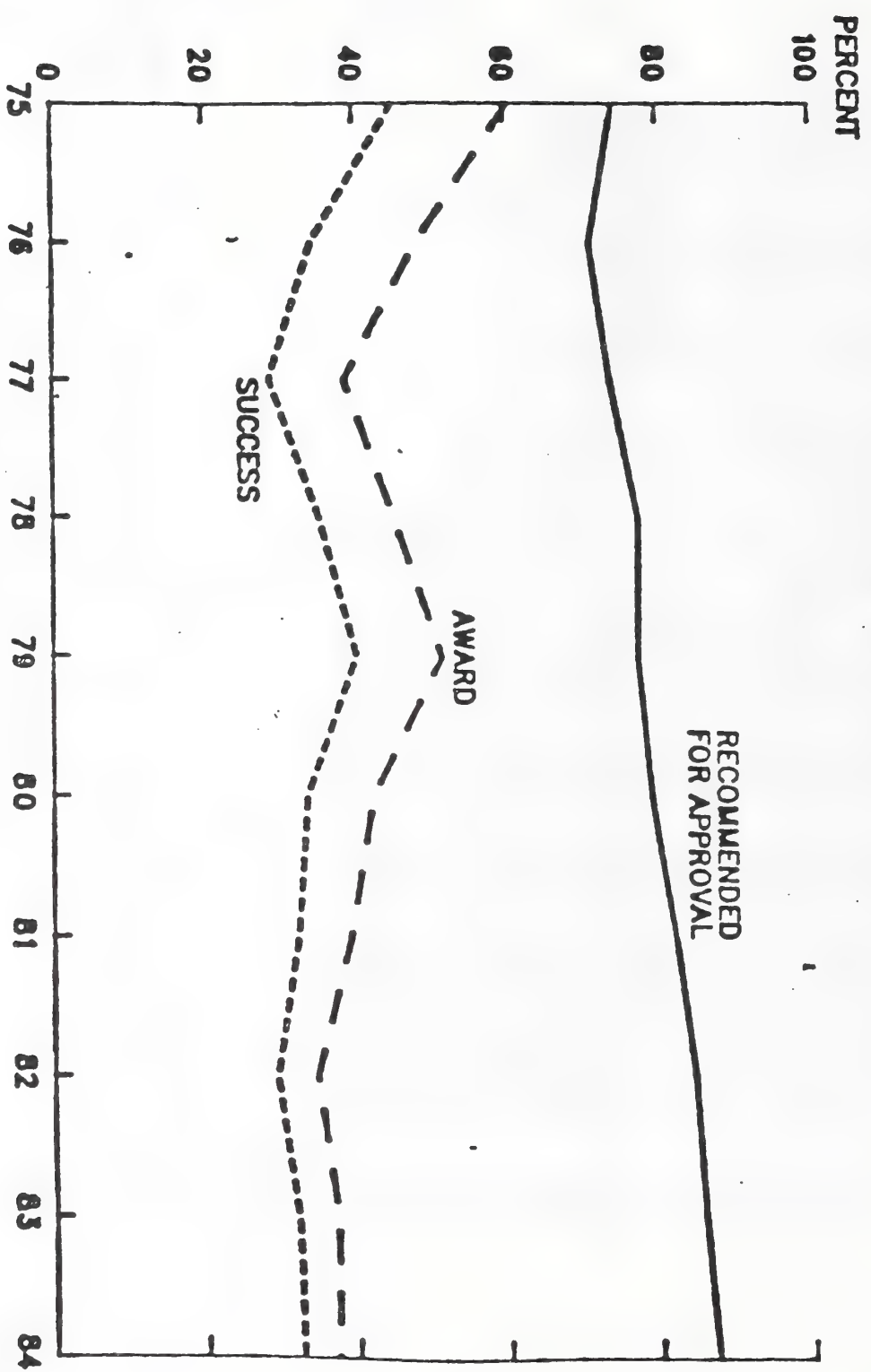
\*EXCLUDES SUPPLEMENTS.  
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

8603-JEC001

61

COUNCIL RECOMMENDED FOR APPROVAL, AWARD, AND SUCCESS RATES  
FOR NUMBER OF NIH RESEARCH PROJECT APPLICATIONS  
FISCAL YEARS 1975-1984

10.7.



## INTRODUCTORY REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

Ladies and Gentlemen,

I would like to welcome all of you this evening to the NIH Lecture. The NIH Lecture Series was established in 1953 to recognize outstanding scientific accomplishment and to contribute to the vital interchange of scientific information. We are very pleased to have with us tonight Dr. Philip Leder, who since 1980 has been the John Emory Andrus Professor of Genetics and Chairman of the Department of Genetics at the Harvard Medical School.

Dr. Leder is a much welcomed and honored speaker at the NIH. He is a native Washingtonian whose career early on was involved with this institution. During his undergraduate years at Harvard University he was a summer student at the NIH in the Laboratory of Cellular Physiology and Metabolism of the National Heart Institute.

Following graduation from Harvard Medical School in 1960, Dr. Leder was an intern and resident at the University of Minnesota Hospital in Minneapolis. In 1962 he rejoined the NIH as a research associate in biochemical genetics in the National Heart Institute under Marshall Nirenberg. In 1965-66, he spent a year in Israel at the Weizmann Institute, after which he returned to NIH to the Biosynthesis Section of the Laboratory of Biochemistry of the National Cancer Institute. Three and a half years later he joined the National Institute of Child Health and Human Development as Head of the Section on Molecular Genetics, Laboratory of Genetics. From 1972 to 1980 he was Chief of the Laboratory of Molecular Genetics.

While at NIH, Dr. Leder served as Vice-President and President of the Foundation for Advanced Education in the Sciences as well as chairman of its Department of Biochemistry. Also while here he gave one of the Mider Lectures.

Dr. Leder is a member of the National Academy of Sciences (NAS) and a recipient of many prestigious awards, including the Richard Lounsbery Award of the National Academy of Sciences and the American Association of Medical Colleges Award for Distinguished Research in the Biomedical Sciences.

---

\*For Dr. Philip Leder at an NIH Lecture on May 19, 1986, in Masur Auditorium.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



He is especially proud of his most recent honors--two honorary Doctor of Science degrees--in 1984 from Yale University and in 1985 from Mount Sinai Medical Center.

Dr. Leder's talk tonight will be on "Misplacing Genes" in which he will discuss the use of transgenic mice as a model for studying the action of oncogenes in the development of cancer. Transgenic mice are created by introducing foreign DNA sequences into the germ line genome. The transgenic system should prove to be an extremely useful tool for delineating the events and the genes that control normal and abnormal cell growth.

Please join me in welcoming Dr. Leder to this, his second, NIH Lecture. So far as we know, Phil, you are the only person to give two NIH Lectures.

RESEARCH: INTERNATIONAL COOPERATION AND COMPETITION\*

BY

JAMES B. WYNGAARDEN, M.D.\*\*

I am very happy to have the opportunity to participate in this session on international cooperation in AIDS research. Continued international collaboration is vital if we are to maintain our momentum toward conquering AIDS, particularly because epidemiological studies outside of the U.S. provide tantalizing clues that may lead us to a better understanding of transmission of the causative agent and contribute to strategies for preventing the disease--now recognized as a problem worldwide.

As many of you know, NIH's commitment to international cooperation in research goes back to its very origins. As NIH approaches its centennial anniversary, and we begin to delve into our history, it has become clear that many of the basic principles upon which NIH was founded are sustained today. One of these tenets is the recognition that biomedical research knows no geographical or political boundaries. In fact, our predecessor organization--the Laboratory of Hygiene-- was established on Staten Island in 1887 because the Congress felt it necessary to create a research laboratory to study diseases that were international in scope and that had

---

\*Speech Presented at a Symposium, "AIDS: Impact on Public Policy, Sponsored by the State of New York Department of Health, N.Y., May 28, 1986.

\*\*Director, National Institutes of Health, Bethesda, Maryland.

serious effects in the United States. Among these were cholera, yellow fever, and tuberculosis. Because European laboratories were at the time the recognized leaders in biomedical research, the first Director of the Laboratory of Hygiene, Dr. Joseph Kinyoun, traveled to Europe to study under Dr. Robert Koch, where he learned the new techniques for isolation and identification of bacteria, and to the Pasteur Institute in France, where he studied methods of preventing rabies. So from its very beginning, NIH has been cognizant of the international nature of biomedical research and has sought to encourage and foster both formal and informal cooperative research efforts.

Many of NIH's programs to enhance international cooperation in biomedical research are focused in its Fogarty International Center (FIC), established in 1968. Through its international studies program, FIC addresses problems concerning international aspects of biomedical and behavioral research, research manpower training, and the transfer of research results. Examples of work conducted under this program include a series of international studies to evaluate available research and its potential applicability to eradicate diseases including measles, polio, and yaws. Other recent collaborative efforts include a meeting on state-of-the-art research related to oncogenes, cell growth, and cancer, and a conference on information processing and medical imaging that brought together 100 researchers from five continents.

The FIC Scholars-in Residence Program, mandated in 1967, enables distinguished scientists and established scholars to interact with NIH intramural scientists for periods of up to one year on subjects relating to international health. These senior scientists, the majority from western Europe, North America, Japan, and Asia, help to establish points

of collaboration between institutions in various countries. It was through this program that Dr. William Jarrett, a well-known expert on animal retroviruses from Glasgow, came to work with NIH (NCI) scientists studying the development of antibodies to various components of the AIDS virus. Dr. Ian Gust, Director of the Medical Research Center at the Fairfield Hospital in Melbourne, is another FIC Scholar concentrating on AIDS. His observations about the pattern of AIDS in Australia have been intriguing to NIH scientists because it differs dramatically from the pattern in the U.S. In Australia, a higher fraction of AIDS cases arise from blood transfusion, while there are very few cases as a result of IV drug use.

Other FIC programs bring foreign postdoctoral scientists to the United States to work with U.S. scientists on problems of mutual interest and send U.S. scientists abroad for study. Some 100 foreign scientists are brought here annually under this program, while approximately 50 U.S. researchers are sent abroad each year.

The NIH intramural research program also attracts talented scientists from around the world, who come to Bethesda to share in the resources of the NIH. Distinguished scientists at varying levels in their careers are invited to receive further training or to conduct research in their biomedical specialities. Stipends are provided, and each participant in the visiting program works closely with a senior NIH investigator who serves as sponsor or supervisor during the visitor's period of appointment. Currently, more than 1,100 scientists from 70 countries are participating in our visitors' programs, with highest representation from Japan, the United Kingdom, Italy, India, and Israel. An additional 400 guest workers also participate in research at the NIH, getting laboratory space and research support, but no stipend. These programs, over the



years, have created an international network of scientists who continue to collaborate with their NIH counterparts throughout their scientific careers. At present, there are 25 foreign Nationals working in collaboration with NIH scientists in the two NIH laboratories that are devoted entirely to AIDS research.

In addition to these programs, which operate primarily through the Fogarty International Center, the individual research institutes of NIH all engage in international projects that take advantage of research opportunities existing abroad. These projects and programs contribute not only to our scientific knowledge base, but also to improving health in the geographic area of interest. Well-known examples include the work of NIH's Dr. Carleton Gajdusek on the slow virus causing the disease kuru in New Guinea. Another example is the NIH study at Lake Maracaibo, Venezuela, where an extended family of 3,000 with a very high rate of Huntington's Disease has been identified. This Venezuela family represents the largest living concentration of the genetic disease in the world and is a great resource in the search for the defective gene in Huntington's Disease.

Similar opportunities seem to exist with regard to AIDS, particularly in certain parts of Africa. But before discussing those epidemiological findings, I would like to provide a bit of background on NIH's overall efforts in approaching the AIDS problem.

The NIH and the scientific community in this country have been able to respond to AIDS in a remarkable way because of an enormous investment in fundamental research over the years. By the time the first AIDS cases were recognized in March and April of 1981--by scientists at UCLA supported by the NIH--that prior investment in basic research had already

generated a wealth of fundamental knowledge in such areas as immunoregulation, basic virology, opportunistic pathogens, the retroviruses, and DNA recombination. Without the benefit of these modern understandings and technologies, it would have been impossible even to identify and characterize AIDS. In addition, a long standing national commitment to training research scientists--both M.D.'s and Ph.D.'s assured a cadre of prepared researchers around the country who were ready to apply their expertise to the challenges posed by AIDS.

With these resources in place, along with a strong intramural research program, NIH was prepared to respond to the emerging epidemic.

The NIH intramural research program was prepared to take an early lead, partly because intramural resources are administratively easier to refocus than extramural mechanisms and partly because NIH was fortuitously endowed with recognized experts in areas related to AIDS. Dr. Anthony Fauci, now Director of the National Institute of Allergy and Infectious Diseases, at that time was Chief of NIAID's Laboratory of Immunoregulation, as well as an authority on the immune system in health and disease. The other major figure was DR. Robert Gallo, of NCI, who in 1979 had reported the first isolation of a human RNA tumor virus, called HTLV-I, which, apparently was associated with adult T-cell Leukemia (ATL) and acquired by infection rather than genetic transmission. Dr. Gallo built this major advance upon his earlier work--the discovery of T-cell growth factor (now called interleukin 2)--which enabled the long-term culture of relatively mature T-cells, which in turn enabled the identification of HTLV-I in T-cell lymphoma cell lines. But the significance of Dr. Gallo's findings could not have been explored absent international collaborations. The availability of Gallo's system offered

the opportunity for seroepidemiologic studies demonstrating the endemic nature of HTLV-I in areas of Japan, the West Indies, Southeast USA, China, the USSR, Africa, Malaysia, and Central and South America. Although adult T-cell leukemia does not rank as a major health problem in the United States, the contributions Dr. Gallo made to our basic knowledge about retroviruses obviously were enormous. Shortly thereafter, as Dr. Gallo turned his attention toward the problem of AIDS, the payoff was rapid.

Early on, the NIH included the extramural community in accelerated efforts to learn about the new disease. Supplemental awards were made by the National Cancer Institute to scientists already supported by NIH so that their research could be redirected toward AIDS. This early effort to encourage research on aids by extramural investigators required diverting funds from other NIH programs because no money had been appropriated for AIDS research.

A number of workshops were held to bring together NIH researchers and scientists nationwide--with recognized experts from abroad--to discuss preliminary research leads and to develop a course of research action. While the scientific community began to initiate studies on the causes of AIDS and some outstanding researchers turned their attention to the problem, NIH began to stimulate research on various aspects of AIDS through issuance of specific Requests for Applications.

Research advances rapidly followed the discovery of the causative agent for AIDS. They included: a description of the underlying immune defects characteristic of the disease; the development of tests for screening donated blood; improved understanding of the modes of transmission; development of methods for processing blood products used by hemophiliacs; complete deciphering of the genetic code of the causative

virus; and recognition that the brain is a primary site of infection. We have also learned a great deal about how the virus infects cells, about the antibodies produced by most people infected with the virus, and about the mechanisms by which the virus propagates. Many of these advances have laid important groundwork for our current challenges--development of therapeutic agents and vaccines.

In terms of budgetary response, funding for AIDS has expanded rapidly. In 1982, the Public Health Service allocated \$5.5 million for AIDS programs, with \$3.4 million for NIH; in 1986, NIH's total obligation for AIDS research is estimated at about \$134 million. It is interesting to note the change in the proportion of funds spent on AIDS intramurally and in extramural programs over the past five years--in 1982, 53% of the funds were spent on intramural AIDS studies and 47% extramurally. By 1986 the proportions had gradually shifted so that only 23% of the now much larger AIDS budget is allocated to intramural studies while 77% is allocated to extramural projects. The change in the relative proportions--extramural to intramural--is seen as a natural evolution reflecting increased interest in AIDS research within the scientific community.

At present, NIH's AIDS research program is emphasizing the development of agents to treat the disease and vaccines to prevent it, with adjuvant studies of basic research on pathogenesis and natural history.

The Public Health Service, through both NIH and the Centers for Disease Control (CDC) has been interested in doing epidemiologic studies of AIDS in various parts of Africa since 1983 when clinicians in Brussels and Paris reported AIDS-like illnesses and T-Cell abnormalities among



African patients without any known lifestyle risk factors for AIDS. These observations led investigators to Rwanda and Zaire, where the patients seen in Belgium had lived and where other patients with similar abnormalities were discovered. After the causative retrovirus for AIDS was determined, studies in Africa quickly confirmed that the same virus was causing the disease in Africa as in the U.S. and Europe.

The data gathered from African population studies thus far are providing clues as to the emergence of AIDS in that continent. These studies are important because if HTLV-III/LAV and AIDS are new to Africa and only now being disseminated, then it becomes urgent from a public health standpoint to understand the mechanisms by which this agent is being spread and to institute control measures.

The NIH is currently supporting, in collaboration with the CDC, a project to study AIDS in Zaire. Studies in African populations have great importance in better understanding the disease in the United States. In contrast to the United States, where most cases are in homosexual males, the ratio of male to female cases in Zaire is 1:1, and there is strong evidence for heterosexual transmission. Information on the transmission of the disease in Africa may be an important indicator of the potential for a greater degree of heterosexual transmission in the U.S. In addition, studies of the cofactors involved in the development of AIDS in Africa may give clues to cofactors involved in the disease elsewhere.

The search in Africa for a progenitor agent from which the AIDS virus may have mutated or with which it may have recombined is also of critical importance. Studies of the differences between this ancestor virus and the current AIDS agent could provide data that would indicate which portion of the genome confers the pathogenic potential, information that

would be useful in designing better therapies for AIDS. In addition, the non-pathogenic progenitor could be examined as a source for a safe immunizing material provided there is any neutralizing cross-reactivity between the two agents. To date, this putative progenitor has not been identified, although there is some evidence pointing toward an agent in African green monkey which is cross-reactive with HTLV-III/LAV.

Additional NIH-supported studies are beginning in prostitutes in Kenya, with direct relevance to similar studies being conducted within the U.S. In the next few years, NIH expects to undertake several other important studies in other countries: natural history studies in homosexual populations in the Caribbean and in Asia (Thailand and Singapore); natural history studies of heterosexually transmitted AIDS in Zaire; prospective studies of AIDS in female prostitutes in Kenya, Trinidad, Jamaica, Surinam, Zambia and Thailand; studies of vertical transmission from mother to newborn, which is common in Africa; studies on cofactors such as parasitic infections and their role in the development of the disease; the identification of nonhuman primate reservoirs in Africa; and studies of racial/genetic factors that may influence acquisition of infection and expressions of disease, for example, studies of the unexplained difference in the rate of disease in those of African versus Asian descent in Trinidad.

International cooperation has been a feature of AIDS research dating from the time the syndrome was recognized as an infectious disease, not only because of the obvious public health issue involved, but also because of the nature of biomedical research and a tradition that demands that scientists be constantly up to date on the cumulative knowledge base in their fields.

International conferences have always been fruitful mechanisms for the interchange of ideas in biomedical research, and this has been the case for scientific subjects relating to AIDS. For example, in January of this year, the NIH and the Association pour la Recherche sur le Cancer sponsored an international symposium in Martinique on virus-associated cancers, bringing together many world renowned virologists, epidemiologists and clinicians concerned with retrovirus research and AIDS. This meeting was an extension of a similar symposium sponsored by the French institution on virus-associated cancers in Africa. A number of international conferences specifically aimed at bringing together scientists concerned with AIDS have been held over the past five years. For example, in 1983, the Pan American Health Organization and the NIAID sponsored a regional meeting on AIDS in the Americas which included public health officials from North, South, and Central America. Just last week in Bethesda, NIH epidemiologists participated in a workshop in AIDS in Africa set up by the Armed Forces Institute of Pathology.

Many of you are already aware of the First International conference on AIDS held in Atlanta in 1985, sponsored primarily by the U.S. Public Health Service with assistance from WHO. The Second International Conference on AIDS, which will draw a large number of U.S. scientists, is to be held next month in Paris, primarily sponsored by French institutions. NIH will be the location for the Third International Conference on AIDS, to be held in June of 1987. Planning for that meeting is already under way.

Another formal mechanism to encourage international cooperation on AIDS is set up by WHO. NIH, the Centers for Disease Control, and the Food and Drug Administration, as well as other organizations around the world

are formally recognized as WHO Collaborating centers on AIDS, responsible primarily for enhancing information exchange aimed at developing international collaboration, training of laboratory personnel in specialized techniques, providing reference reagents, evaluating diagnostic tests, and organizing activities to determine the natural history of the disease in different parts of the world.

These formal efforts to enhance international cooperation aside, probably the most fruitful collaborations are those worked out by individual scientists sharing information, biological samples, and expertise. As additional countries become concerned about the spread of AIDS, it is becoming more and more common to see papers relating to AIDS in the scientific literature bearing the names of scientists from two or even more countries. It is not at all uncommon for the NIH weekly calendar of lectures to list at least one or two scientists from abroad speaking on some aspect of AIDS research. The level of interchange I see taking place on almost a daily basis leads me to believe that it would be impossible to stop such cross-fertilization--such is always the case and should be the case with a biomedical research opportunity as fruitful as AIDS and a public health problem as compelling as this.





MEDICINE AS ART: MEDICINE AS SCIENCE\*

by

James B. Wyngaarden, M.D.\*\*

Next year the National Institutes of Health will observe its 100th birthday. "A Century of Science for Health" will be the subject of seminars, symposia, ceremonies and salutes of different kinds beginning in October of this year and continuing through October of next. Obviously, we are excited about the plans for our celebration, but I will be duly respectful of your institutional seniority clearly established by the fact that this is your 165th commencement exercise. I had another opportunity to practice such humility a few weeks ago when I participated in a centenary celebration of the founding of Heidelberg University. Rather than marking the events of a single century as NIH will be doing, however, Heidelberg was observing its 600th anniversary. I could not resist mentioning the NIH centennial there, but you may be sure that I did it with a certain deference.

I have a valid reason for returning to our institutional history on this occasion because an important chapter of it, lasting almost a third of a century, was played out within a few blocks of here.

The NIH came into being at a time when medical science in the United States lagged behind the state of knowledge in Europe. Studies in the new discipline, bacteriology, led by Robert Koch and Louis Pasteur, were taking place in many European laboratories, but not many Americans participated in those advances. A yellow fever epidemic in 1878 had created widespread alarm and a variety of measures were proposed for its prevention and control--none particularly effective. Other communicable diseases, such as cholera and tuberculosis were also matters of grave concern. Because travelers and immigrants were thought to be bringing these diseases into

---

\*Commencement address given at the George Washington University School of Medicine and Health Sciences, Washington, D.C., May 30, 1986.

\*\*Director, National Institutes of Health, Bethesda, Maryland

our country, efforts to arrest the spread of contagion were concentrated at ports of entry. Thus in 1887 a one-room laboratory was set aside in the Marine Hospital on Staten Island in the Port of New York and it was dedicated to research on communicable diseases. Called the National Laboratory of Hygiene, this modest facility ultimately became the National Institutes of Health. In 1891 the laboratory was moved to Washington to a building on Capitol Hill, which it occupied about twelve years before moving to 25th and E, the nearby site of which I spoke a moment ago, and there it stayed for about 35 years.

Among the scientists associated with the Hygienic Laboratory were some of the heroes of medicine. For example, Dr. Howard Taylor Ricketts whose work on Rocky Mountain spotted fever provided the key for finding the cause of one of the great plagues of mankind--epidemic typhus. Ricketts died of typhus in 1910 a victim of the organism that he had earlier described and that subsequently was named for him--the Rickettsia.

In 1912 Dr. T. B. McClintock was sent from the Hygienic Laboratory to Montana to carry out a project that had been planned by Dr. Ricketts. He completed the project, but contracted spotted fever and died shortly after returning to Washington.

The Hygienic Laboratory had one of its most dramatic and deadly crises in 1929 when an outbreak of psittacosis occurred simultaneously in three continents, Europe, North America and South America. Even scientists in this country scarcely knew there was such a disease as psittacosis. It seemed to have been spread by a shipment of diseased parrots in the Christmas trade from a South American port. Suspect parrots were brought into the Hygienic Laboratory from nearby cities and from as far away as Maine and Ohio. Within three days after the birds were brought into one of the basement laboratories, Henry Anderson, the assistant to the laboratory chief, was hospitalized and in a few days he died of psittacosis. There was at least one more death from the disease and several of the leading scientists in the laboratory had been seriously ill.

A giant among the remarkable members of the staff of the Hygienic Laboratory was Dr. Joseph Goldberger. Considered to be one of the most promising of the young men connected with the Hygienic Laboratory he was placed in charge of the Public Health Service investigation of pellagra, then prevalent in the poverty-stricken South, but known as a problem in 40 states as well as the District of Columbia. The Public Health Service was determined to make an attack on pellagra thought by most medical scientists of the time to be caused by a particular organism. Dr. Goldberger argued that if a bacillus were the cause, some of the doctors and nurses and other attendants working around the pellagra patients daily would get it too. He pointed out that the one difference between the inmates in prisons and mental institutions, and the people who cared for them was their diet--yet, many of the inmates suffered from pellagra, their attendants did not. Dr. Goldberger's confirmatory investigation was a classic of epidemiology. He was a master of both observation and experimentation. Goldberger and his associates showed that the poor, monotonous diets common to many low-income people--diets high in carbohydrate and low in good quality protein and fresh vegetables--induced pellagra when fed to volunteer convicts in a Mississippi penitentiary. In other public institutions where the disease occurred, these investigators demonstrated that generous amounts of milk, eggs, meat, beans, and peas prevented it. Still, physicians who were treating pellagra at the time strongly believed that it was due to an infectious organism and would not accept Goldberger's evidence.

As a final proof that no infectious mechanism was involved, Goldberger and one of his collaborators injected each other with blood from a pellagra patient. Later Goldberger and four associates swallowed capsules containing patients' wastes and skin scrapings, and Goldberger injected blood from a pellagrous woman into his wife, Mary. None contracted the disease, though it is not recorded what adverse symptoms may have resulted from these heroic experiments.

He later developed a treatment using yeast in the diet and showed that the amino acid tryptophan was crucially related to the cause of the disease. Soon the B. vitamin nicotinic acid, now called niacin, was identified as a specific pellagra preventive. From these beginnings an interest in other



aspects of nutrition evolved, particularly in the constituent institute of NIH concerned with arthritis and metabolic diseases. Other nutrients and facts about nutrition were discovered both in experimental animals and man.

Interest in the field waned somewhat as more promising research areas developed. Molecular biology, immunology, virology, and cell biology proved more attractive to many young investigators. In recent years, however, there has been a resurgence of certain aspects of nutrition research, particularly those relating to specific diseases. Thus, nutritional aspects of atherosclerosis, certain cancers, diabetes and other endocrine disorders, osteoporosis, and obesity have all been subjected to important inquiries in the laboratories and clinics of NIH, as well as in many research institutions throughout the Nation in studies supported by the National Institutes of Health.

In remembering the work of Joseph Goldberger, my mind turned to a trenchant observation by my longtime friend and collaborator Dr. Lloyd H. Smith, Jr., who recently retired as chairman of the Department of Medicine at the University of California in San Francisco. His essay on "Medicine as an Art" in the Cecil Textbook of Medicine began with descriptions of aspects of medicine. One defined its boundaries as blending into psychology, sociology, economics, and even into cultural heritage. He could well have been referring to the lessons learned from pellagra when he added that, "Disease may be encoded in the genome; disease may also be encoded by the deprivations of poverty and ignorance."<sup>1</sup>

He then went on to summarize, "The practice of medicine as an art is far more than the application of scientific principles to a particular biologic aberration. Its focus is on the patient whose welfare is its continuing purpose." Although they were concerned with the broad problems of public health, the heroes of the Goldberger era were practitioners of both the art and the science of medicine. Their focus on groups of particular patients took the form of what has been described by Walsh McDermott as "statistical compassion."

Since the days of the Hygienic Laboratory the powerful measures available to the health care professional for prevention, diagnosis, and treatment of disease have increased to an extent that probably would have been unimaginable to the most visionary of the physician-scientists of the early 1900s. Within the span of less than 50 years, antibiotics were introduced; the function and structure of DNA were elucidated, and now can be manipulated; the science of immunology was established; transplantation of human organs has become feasible; and new and extremely effective methods for diagnostic imaging have been developed. Yet with all this progress the practice of medicine continues to be both an art and a science.

A skilled physician today must have extensive medical knowledge which is the bedrock of technical competence. In addition, he or she must have judgment, tact, decisiveness, restraint, compassion, interest, time and other personal qualities of caring and dedication. The science and the art of medicine must always be intimately linked. The student studies the science of medicine first, masters it early, and returns to it frequently. The student acquires the art of medicine--the skillful application of medical knowledge in the optimal care of the patient--more gradually and with experience.

If one were to be limited to one word to describe the essential qualities of a physician that word might be competence in its broadest application.

Since medicine is derived from a number of sciences relevant to the health of individuals and groups, physicians must be competent scientists to utilize these complex disciplines effectively. This implies that the physician must have more than rote scientific knowledge or even fluency in its particular jargon. Physicians must be conversant with the processes of scientific inquiry--how data are obtained and evaluated; how hypotheses are framed, modified, or discarded; the uses and limitations of inductive reasoning. In short, they must understand science as an intellectual instrument that has slowly been perfected over centuries.

As a scientist the physician is the beneficiary of both the fruits of scientific research and of the mental discipline of the scientific method.

While I have addressed these comments specifically to the physician, they apply with equal validity to all professional members of the health care team.

Permit me to turn now to some general comments about some of the recent fruits of science that are, or will be, of significant importance to all members of today's graduating classes.

In a large measure as a result of the development of the government-academic partnership in research, there has been amassed a spectacular store of biological knowledge. But the biological revolution is far from over and, in fact, is now approaching major questions with immediate relevance to human health. Key discoveries in molecular biology, genetics, and immunology have led to the widespread use of techniques that are enabling scientists to address fundamental questions about the nature of living organisms.

Cells and bacteria can be transformed into factories to produce custom-made monoclonal antibodies, polypeptide hormones and growth factors. Soon such cellular factories may be producing highly selective second or third messengers for very precise therapeutic effects. For example, instead of prescribing a steroid such as cortisone, you may be selecting a particular molecular effector from among the many that cortisone evokes for a very precise physiological or pharmacological action.

Competence in today's health care practitioner implies familiarity with and ability to use many of the powerful tools and techniques that have been developed in the course of the explosion of new knowledge, or tools whose development can be expected in the reasonably near future.

It seems clear that biomedical research fuels technology which in turn seems to be offering up more and more advances with direct application in the health care setting. The pace of these advances is accelerating and



exhilarating! This phenomenon raises concerns about the possible impact of biomedical research upon the cost of medical care, a matter about which health care professionals must be informed.

Many highly technical procedures for diagnosis and treatment now coming into frequent use are truly miracles of modern medicine, but often they are very expensive and constitute a powerful force driving upward the cost of medical care. In the context of these developments, we encounter a paradox; namely that a substantial number of medical discoveries in recent years have increased rather than decreased the cost of medical care. Experts in health care and research are warning that costly medical procedures--coronary bypass surgery, sophisticated new imaging systems, heart and liver transplants--could result in vast additional health outlays in the next decade. Thus we are confronted with two challenges; first, to continue research that will bring us beyond the highly expensive halfway point in treatment of disease--as has been the mission of NIH and its academic partners. The second challenge is to develop data that more clearly demonstrate that biomedical research contributes to cost savings in health care.

I recently asked the various NIH components to provide some examples of advances from biomedical research of the past decade that have reduced health care costs. You may be interested in some of the examples and the estimates of savings for which they are responsible.

- o Research in San Francisco supported by the National Heart, Lung, and Blood Institute (NHLBI) conducted on sheep implicated prostaglandins in maintaining patency of the ductus arteriosus. This led to treatment of newborns having the patent ductus syndrome with the prostaglandin synthetase inhibitor, indomethacin, for medical closure of the ductus. This treatment is successful in about 85 percent of cases. We estimate that use of indomethacin as a substitute of surgical treatment saves approximately \$180 million annually.



- o The National Eye Institute estimated savings of about \$154 million annually from laser treatment of angle-closure glaucoma, aging related maculopathy, and diabetic retinopathy.
- o Our research-derived ability to assess fetal maturity makes it possible to prevent prematurity associated with cesarean delivery, thus saving about \$325 million a year.
- o Based on the Coronary Artery Surgery Study, we estimated that 25,000 coronary bypass operations could have been deferred in 1983 with a potential reduction in health care costs of nearly \$500 million.
- o Antenatal steroid therapy in high risk pregnancies to prevent neonatal respiratory distress syndrome would save about \$295 million per year.

From the limited list of examples provided me by the institutes--of which I have mentioned only a few--we estimate savings in health care costs of approximately \$2.5 billion annually. That is almost half of the total 1986 budget for the NIH.

Commencement is a time for looking back as well as forward. It is a time when we can see the years of preparation for this milestone with a clearer perspective than before. There is more than sentimental value in such a retrospective for the way we regard these past years can have an effect on the years to follow. The widely respected medical educator Alan Gregg once proposed a useful though subtle measure when he said, "A good education should leave much to be desired." He commented, "Honors and degrees carry too little expectancy; they have the general odor of receipted bills, certificates of past performance, or rewards or honorable scars or epitaphs."<sup>2</sup>

Earlier I characterized competency as the essential qualification of a health professional. You who are graduating have acquired an impressive level of competency which will expand greatly in the next few years as you gain experience giving care to patients. The enemy of competency is complacency which has been called the "dry rot of medical competency."

Competency in medicine is always both partial and provisional; it is biodegradable but also infinitely renewable by those who remain lifelong students of medicine. That is, in fact, the meaning of "commencement." It is another beginning.

Congratulations and best wishes for a productive and satisfying life.

#### REFERENCES

<sup>1</sup>Lloyd H. Smith, Jr., M.D., "Medicine as an Art,"  
Introductory Essay to Cecil Textbook of Medicine,  
16th Edition, p. xxxiii.

<sup>2</sup>Alan Gregg, M.D., as quoted by Lloyd H. Smith,  
"Medical Education for the Twenty-First Century,"  
UCSF Magazine (University of California San Francisco),  
June 1985, p. 46.



## REPORT ON NIH ACTIVITIES\*

BY

JAMES B. WYNGAARDEN, M.D.\*\*

EARLY SPRING IS THE SEASON FOR THE ANNUAL BUDGET HEARINGS FOR AGENCIES OF THE UNITED STATES GOVERNMENT. THE NATIONAL INSTITUTES OF HEALTH APPEARED BEFORE THE APPROPRIATIONS COMMITTEES OF THE CONGRESS IN MARCH TO EXPLAIN AND DEFEND THE AMOUNTS REQUESTED BY THE PRESIDENT FOR THE OPERATIONS OF THE AGENCY DURING FISCAL YEAR 1987.

THIS YEAR THE FEDERAL DEFICIT AND THE EFFORT OF THE CONGRESS AND THE ADMINISTRATION TO DEAL WITH IT HAVE AFFECTED ALL COMPONENTS OF THE GOVERNMENT.

WITHOUT DISCOUNTING IN ANY WAY THE CURRENT PROBLEMS AND FORESEEABLE DIFFICULTIES, I CONTINUE TO BE AN OPTIMIST ABOUT THE FUTURE OF BIOMEDICAL RESEARCH IN OUR COUNTRY, AND IN PARTICULAR ABOUT THE PROSPECTS FOR THE NATIONAL INSTITUTES OF HEALTH. DESPITE CURRENT FISCAL PRESSURES, IT IS MY CONVICTION THAT WE CAN BE CONFIDENT OF THE FUTURE OF THE NIH. I BASE THIS BELIEF ON THE STRONG AND STEADY COMMITMENT OF BOTH THE EXECUTIVE AND THE LEGISLATIVE BRANCHES OF THE FEDERAL GOVERNMENT TO THE SUPPORT OF BIOMEDICAL RESEARCH.

---

\*PRESENTED AT THE MEETING OF THE EUROPEAN MEDICAL RESEARCH COUNCIL IN LONDON, JUNE 5-6, 1986.

\*\*DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND



THE PRESIDENT'S BUDGET REQUEST FOR FISCAL 1987 FOR NIH IS APPROXIMATELY \$4.9 BILLION. THIS IS A DECREASE OF ABOUT 4 PERCENT FROM THE CURRENT OPERATING LEVEL OF THE AGENCY. ABOUT 1.5 PERCENT OF OUR TOTAL BUDGET IS DEVOTED TO INTERNATIONAL ACTIVITIES.

HISTORICALLY THE CONGRESS HAS ACTED TO INCREASE THE TOTAL FUNDING FOR THE NIH BY SUBSTANTIAL AMOUNTS ABOVE THE PRESIDENT'S REQUEST. OVER THE PAST FOUR YEARS THOSE INCREASES HAVE RANGED FROM 6.8 PERCENT TO 13.3 PERCENT, AVERAGING SOMETHING MORE THAN 10 PERCENT.

AS IN PREVIOUS YEARS, OUR BUDGET PLANS GIVE HIGHEST PRIORITY TO INVESTIGATOR-INITIATED RESEARCH GRANTS. MORE THAN 57 PERCENT OF OUR TOTAL BUDGET FOR 1987 IS ALLOCATED TO THE SUPPORT OF INVESTIGATOR-INITIATED RESEARCH PROGRESS.

THE NEW BUDGET PROPOSAL WOULD ESTABLISH A CONTINUING POLICY OF FUNDING A TOTAL OF AT LEAST 18,000 NEW, COMPETING RENEWAL, AND CONTINUING GRANTS EACH YEAR. IT IS HEARTENING THAT THE WHITE HOUSE SET THE STABILIZATION LEVEL AT 18,000 TOTAL GRANTS, INASMUCH AS THAT IS VERY NEAR THE HIGHEST NUMBER IN NIH HISTORY--18,319 REACHED IN 1985.

NOTWITHSTANDING OUR FUNDING OF THIS NUMBER OF GRANTS, THE NUMBER OF APPLICATIONS FOR GRANTS HAS GROWN EVEN FASTER THAN OUR RESOURCES. IN 1975 WE WERE ABLE TO FUND ABOUT 65 PERCENT OF GRANTS ELIGIBLE FOR AWARD, BUT IN 1984 AND 1985 THE AWARD RATE WAS ONLY ABOUT 37 PERCENT.

ALTHOUGH FISCAL RESTRAINTS HAVE BEEN RESPONSIBLE FOR DIFFICULTIES EXPERIENCED BY RESEARCHERS IN ACQUIRING RESEARCH SUPPORT FROM THE NIH, CERTAIN ASPECTS OF OUR AWARD SYSTEM MAY BE MORE BURDENSOME THAN NECESSARY FOR THE INVESTIGATOR, THE UNIVERSITY, AND THE NIH PEER REVIEW SYSTEM.

ONE OF THE FACTORS IS THE EXCESSIVE COMPLEXITY AND SHEER BULK OF THE RESEARCH GRANT APPLICATION. WE WILL SHORTLY BE PROPOSING PAGE LIMITATIONS IN GRANT APPLICATIONS. THIS SHOULD REDUCE REVIEWING TIME OF STUDY SECTION MEMBERS AS WELL AS PREPARATION TIME FOR THE APPLICANT.

WE HAVE RECENTLY ANNOUNCED A NEW PROGRAM CALLED FIRST AWARDS (FIRST INDEPENDENT RESEARCH SINCE TRAINING), A MODIFICATION WHICH RAISES THE TERM OF THE INITIAL AWARD FROM 3 TO 5 YEARS, AND THE TOTAL TO \$350,000 OF DIRECT COSTS FOR THE 5 YEARS. THIS SHOULD ORBIATE THE DIFFICULTY FOR YOUNG INVESTIGATORS WHO HAVE OFTEN FOUND IT NECESSARY TO BEGIN THE PPOCESS OF REAPPLICATION AS EARLY AS 18 MONTHS AFTER THE INITIAL AWARD.

WE HAVE ALSO EXPANDED THE NUMBER AND TYPES OF LONGER-TERM SUPPORT FOR OUTSTANDING SCIENTISTS THROUGH A NEW PROGRAM CALLED MERIT AWARDS (METHOD OF EXTENDING RESEARCH IN TIME). THIS PROGRAM WILL INVOLVE FACILITATED EXTENSIONS OF 5-YEAR AWARDS FOR AN ADDITIONAL 3 TO 5 YEARS ON THE BASIS OF A DETAILED PROGRESS REPORT RATHER THAN A FORMAL REAPPLICATION.

A GREATER NUMBER OF LONGER GRANTS TO BOTH FIRST TIME AND ESTABLISHED INVESTIGATORS REPRESENTS, IN OUR VIEW, AN EFFICIENT AND PRUDENT INVESTMENT OF FEDERAL FUNDS THAT SHOULD LEAD TO INCREASED PRODUCTIVITY AND CREATIVITY.

ANOTHER OF OUR HIGHEST PRIORITIES IS RESEARCH TRAINING. THE NIH PROVIDES SUPPORT FOR RESEARCH TRAINING THROUGH A VARIETY OF TYPES OF GRANTS. WE MUST INSURE THAT THERE IS A CONTINUING SUPPLY OF HIGHLY COMPETENT SCIENTISTS COMING INTO THE SYSTEM. WE ESPECIALLY NEED TO ATTRACT YOUNG PHYSICIANS INTO ACADEMIC SCIENCE AND SUPPORT THEIR TRAINING ADEQUATELY BECAUSE THE AVERAGE MEDICAL SCHOOL EDUCATION IS NOT A RESEARCH EDUCATION AT ALL.

AT OUR HEADQUARTERS IN BETHESDA, A HIGHLY EFFECTIVE TRAINING PROGRAM IS CONDUCTED IN OUR OWN LABORATORIES AND CLINICS. ABOUT 2,500 SCIENTISTS WITH DOCTORAL DEGREES AND AS MANY AS 3,500 SUPPORT STAFF MAKE UP THE CORE OF OUR INTRAMURAL RESEARCH PROGRAM. THE DIVERSITY OF THIS PROGRAM IS REMARKABLE, AND THE OPPORTUNITY FOR EXCELLENT TRAINING EXPERIENCE IS COMMENSURATE. AT THIS TIME 886 TRAINEES ARE PARTICIPATING IN THIS REGULAR PROGRAM.

ABOVE AND BEYOND THE REGULAR TRAINING PROGRAM WE CONDUCT THE NIH VISITING PROGRAMS FOR TALENTED SCIENTISTS FROM THROUGHOUT THE WORLD, WHO COME TO BETHESDA TO SHARE IN OUR RESEARCH ACTIVITIES. CURRENTLY OVER 1,100 SCIENTISTS FROM 70

COUNTRIES ARE PARTICIPATING IN OUR VISITORS PROGRAMS.. IN ADDITION, ABOUT 400 GUEST WORKERS ALSO PARTICIPATE IN RESEARCH AT NIH. THESE GUEST SCIENTISTS DO NOT RECEIVE STIPENDS BUT ARE PROVIDED LABORATORY SPACE AND RESEARCH SUPPORT.

A MATTER OF CONCERN TO INVESTIGATORS IN MANY INSTITUTIONS CONDUCTING RESEARCH IN OUR COUNTRY IS THE NEED TO MAINTAIN LABORATORIES AND EQUIPMENT AT THE CURRENT STATE-OF-THE-ART. WE ARE ALSO VERY CONCERNED ABOUT THIS MATTER. A RECENT STUDY HAS INDICATED A VERY SERIOUS SHORTFALL IN SMALL INSTRUMENTS COSTING BETWEEN \$5,000 AND \$60,000. THE SHORTFALL IS GREATER IN STATE-SUPPORTED INSTITUTIONS, WITH A NUMBER OF THE DEPARTMENT CHAIRMEN REPORTING THAT MANY RESEARCH PROJECTS CANNOT BE ATTEMPTED BECAUSE OF LACK OF INSTRUMENTATION. IT IS OUR SENSE THAT FUNDING IN THIS AREA HAS FALLEN BELOW THE CRITICAL LEVEL, AND THAT THE PROBLEM MUST BE ADDRESSED.

MANY INSTITUTIONS IN THE UNITED STATES ARE COMING UNDER PRESSURE FROM A SMALL BUT DETERMINED SEGMENT OF SOCIETY OPPOSED TO THE USE OF ANIMALS IN RESEARCH. THERE HAVE BEEN BREAK-INS AT ABOUT A DOZEN SITES, AND LAST SUMMER A "SIT-IN" WAS HELD IN ONE OF THE NIH OFFICE BUILDINGS. CURRENTLY WE ARE IN THE SECOND MONTH OF A DAILY VIGIL BEING HELD BY AN ACTIVIST GROUP AT ONE OF THE ENTRANCES TO OUR GROUNDS. AT OTHER LOCALITIES THERE HAVE BEEN BOMB THREATS AND VANDALISM AGAINST THE PROPERTY OF INVESTIGATORS AND OTHERS ASSOCIATED WITH STUDIES REQUIRING THE USE OF ANIMALS.



THE NUMBER OF LEGISLATIVE PROPOSALS ON THE SUBJECT AT THE NATIONAL, STATE, AND LOCAL LEVELS IS ON THE INCREASE. THERE IS A CRITICAL NEED TO DEVELOP BETTER UNDERSTANDING AMONG THE GENERAL PUBLIC, THE MASS MEDIA AND ELECTED OFFICIALS ON THE SCIENTIFIC IMPERATIVES OF USING ANIMALS IN RESEARCH.

I AM PLEASED THAT FOUR OF OUR NATIONAL ORGANIZATIONS--THE AMERICAN MEDICAL ASSOCIATION, THE AMERICAN COLLEGE OF SURGEONS, THE ASSOCIATION OF AMERICAN MEDICAL COLLEGES, AND THE AMERICAN PHYSIOLOGICAL SOCIETY--ARE SERVING AS CATALYSTS AMONG SCIENTIFIC, PROFESSIONAL, ACADEMIC AND CORPORATE GROUPS ENCOURAGING DIALOG AND A MORE ACTIVE STAND IN BEHALF OF LABORATORY ANIMAL RESEARCH.

THE FEDERAL-PRIVATE PARTNERSHIP FOR BIOMEDICAL RESEARCH IN THE UNITED STATES CONTINUES TO GROW STRONGER. CONCURRENTLY WITH, AND IN LARGE MEASURE AS A RESULT OF THE GOVERNMENT-MEDICAL SCHOOL PARTNERSHIP THERE HAS BEEN AMASSED A SPECTACULAR STORE OF BIOLOGICAL KNOWLEDGE, NOT TO MENTION TREMENDOUS ADVANCES DIRECTLY RELEVANT TO HUMAN HEALTH--PARTICULARLY THOSE ADVANCES THAT HAVE USHERED IN THE AGE OF MOLECULAR BIOLOGY.

RECOMBINANT DNA TECHNIQUES HAVE MADE IT POSSIBLE TO PRODUCE HUMAN INSULIN IN COMMERCIAL QUANTITIES. TODAY 50 PERCENT OF NEWLY DIAGNOSED DIABETICS WHO REQUIRE INSULIN ARE PUT ON THIS SYNTHETIC TYPE. ANOTHER IS RECOMBINANT HUMAN GROWTH HORMONE, A SUPERIOR AND SAFE SUBSTITUTE FOR THE RARE AND EXPENSIVE PRODUCT

DERIVED FROM HUMAN PITUITARY GLANDS. RECOMBINANT GAMMA INTERFERON FOR USE AGAINST CANCER AND VIRAL INFECTION, AND A SUBSTANCE CALLED TISSUE-TYPE PLASMINOGEN ACTIVATOR--A BLOOD CLOT DISSOLVER FOR CORONARY PATIENTS--ARE IN CLINICAL TRIAL. AGRICULTURAL AND FOOD PROCESSING APPLICATION OF THE NEW TECHNIQUES ARE IN THE OFFING.

A REMARKABLE AND LARGELY UNANTICIPATED ASPECT OF BIOTECHNOLOGY HAS BEEN ITS DIVERSE IMPACT AND POTENTIAL WITH RESPECT TO THE GENERAL ECONOMY. IN THE UNITED STATES IT IS ESTIMATED THAT THERE ARE AT LEAST 200 SMALL COMPANIES SPECIALIZING IN BIOTECHNOLOGY AND MANY LARGE CHEMICAL COMPANIES ARE CONDUCTING RECOMBINANT DNA RESEARCH. IT HAS BEEN ESTIMATED THAT FUTURE SALES OF BIOTECHNOLOGY PRODUCTS WILL REACH BETWEEN \$20 BILLION AND \$100 BILLION ANNUALLY BY THE YEAR 2000.

THE NIH BECAME INVOLVED IN POLICY FORMULATION FOR THE CONDUCT OF THIS NEW SCIENCE LONG BEFORE THE TERM "BIOTECHNOLOGY" WAS A PART OF OUR EVERYDAY LANGUAGE.

ONE CURRENT DEBATE IS OVER THE SAFETY OF THE RELEASE OF DNA RECOMBINANT MATERIALS IN THE ENVIRONMENT IN CONNECTION WITH FIELD TESTING OF BACTERIA GENETICALLY ENGINEERED TO PROTECT PLANTS FROM PROBLEMS SUCH AS FROST DAMAGE OR INSECT PESTS.

A SECOND CURRENT ISSUE IS HUMAN GENE THERAPY USING GENETIC ENGINEERING TECHNIQUES. RECENTLY THE NIH RECOMBINANT DNA

ADVISORY COMMITTEE DEVELOPED AND PUBLISHED A DOCUMENT FOR THE GUIDANCE OF SCIENTISTS CONSIDERING GENE THERAPY RESEARCH IN HUMAN SUBJECTS. SPECIFICALLY EXCLUDED FROM THE DOCUMENT WERE ANY EXPERIMENTAL TREATMENTS DESIGNED TO PRODUCE EFFECTS THAT COULD PASS FROM ONE GENERATION TO THE NEXT.

THE PUBLICATION OF GUIDANCE FROM THE RECOMBINANT ADVISORY COMMITTEE IS AN IMPORTANT STEP IN BRINGING GENE THERAPY INTO PRACTICAL USE AND WILL PERMIT THE SEVERAL SCIENTIFIC TEAMS STUDYING GENE THERAPY TO PROPOSE SPECIFIC TRIALS WITH PATIENTS.

BECAUSE IT HAS BEEN INCREASINGLY A MATTER OF INTERNATIONAL CONCERN, I WILL MENTION BRIEFLY OUR AIDS RELATED ACTIVITIES. RESEARCH ADVANCES RAPIDLY FOLLOWED THE DISCOVERY OF THE CAUSATIVE AGENT FOR AIDS. THEY HAVE INCLUDED: A DESCRIPTION OF THE UNDERLYING IMMUNE DEFECTS CHARACTERISTIC OF THE DISEASE; THE DEVELOPMENT OF TESTS FOR SCREENING DONATED BLOOD; IMPROVED UNDERSTANDING OF THE MODES OF TRANSMISSION; DEVELOPMENT OF METHODS FOR PROCESSING BLOOD PRODUCTS USED BY HEMOPHILIACS; COMPLETE DECIPHERING OF THE GENETIC CODE OF THE CAUSATIVE VIRUS; AND RECOGNITION THAT THE BRAIN IS A PRIMARY SITE OF INFECTION. MANY OF THESE ADVANCES HAVE LAID IMPORTANT GROUNDWORK FOR OUR CURRENT CHALLENGES--DEVELOPMENT OF THERAPEUTIC AGENTS AND VACCINES.

INTERNATIONAL COOPERATION HAS BEEN A FEATURE OF AIDS RESEARCH DATING FROM THE TIME THE SYNDROME WAS RECOGNIZED AS AN

INFECTIOUS DISEASE. WITHIN THESE COOPERATIVE ACTIVITIES, INTERNATIONAL CONFERENCES HAVE ALWAYS BEEN FRUITFUL MECHANISMS FOR THE INTERCHANGE OF IDEAS. THE SECOND INTERNATIONAL CONFERENCE ON AIDS, WHICH WILL DRAW A LARGE NUMBER OF U.S. SCIENTISTS, IS TO BE HELD LATER THIS MONTH IN PARIS, PRIMARILY SPONSORED BY FRENCH INSTITUTIONS. THE NIH WILL BE THE HOST FOR THE THIRD INTERNATIONAL CONFERENCE ON AIDS TO BE HELD IN JUNE OF 1987.

IN CLOSING PERMIT ME TO EXPRESS MY DEEP APPRECIATION TO EACH OF YOU FOR YOUR DECISION TO HOLD NEXT YEAR'S MEETING OF THE EMRC IN BETHESDA. AT THAT TIME WE WILL BE AT ABOUT THE MIDPOINT OF A YEAR-LONG OBSERVANCE OF THE CENTENNIAL OF THE ESTABLISHMENT OF THE NIH. THE NIH HAD ITS BEGINNING IN A SMALL LABORATORY ESTABLISHED ON STATEN ISLAND IN THE PORT OF NEW YORK IN 1887. THE MEETING OF EMRC IN BETHESDA DURING NIH'S CENTENNIAL YEAR IS IN ITSELF SYMBOLIC, FOR THE NEW LABORATORY WAS DEEPLY ROOTED IN THE ADVANCES IN SCIENCE TAKING PLACE IN EUROPE IN THE 1880s. MEDICAL SCIENCE IN THE UNITED STATES LAGGED FAR BEHIND THE STATE OF KNOWLEDGE IN EUROPE, AND THE LABORATORY WAS A FRAGILE TRANSPLANT FROM THE FERTILE FIELDS OF EUROPEAN MEDICAL SCIENCE.

WE WILL CONSIDER YOUR MEETING TO BE A HIGHLIGHT OF OUR CELEBRATION OF "A CENTURY OF SCIENCE FOR HEALTH."





## REMARKS\*

BY

JAMES B. WYNGAARDEN, M.D.\*\*

IN THIS TIME SET ASIDE FOR RECOGNITION OF INDIVIDUAL ACCOMPLISHMENTS, WE ARE MINDFUL THAT THE PERSONS BEING HONORED ARE REPRESENTATIVE OF MANY OTHERS OF OUR COMMUNITY WHOSE ACHIEVEMENTS DESERVE SIMILAR ACKNOWLEDGEMENT.

THE CITATIONS THAT YOU WILL BE HEARING CONSTITUTE EXPRESSIVE FOOTNOTES TO THE MOST RECENT CHAPTER IN THE HISTORY OF THE NATIONAL INSTITUTES OF HEALTH. WE CAN ALL BE PROUD OF THAT HISTORY, AND AS WE NEAR THE BEGINNING OF OUR HUNDREDTH YEAR AS AN INSTITUTION IT IS APPROPRIATE THAT WE SPEND A FEW MINUTES REVIEWING SOME PAGES OF THE FASCINATING ACTIVITIES OF OUR PREDECESSORS.

IN 1903 THE NATIONAL LABORATORY OF HYGIENE, OUR PARENT ORGANIZATION, WAS MOVED TO A LOCATION AT 25TH AND E STREETS, NEAR THE PRESENT KENNEDY CENTER, AND THERE IT REMAINED FOR 35 YEARS. AMONG THE SCIENTISTS ASSOCIATED WITH THE HYGIENIC LABORATORY WERE SOME OF THE HEROES OF MEDICINE. FOR EXAMPLE, DR. HOWARD TAYLOR RICKETTS WHOSE WORK ON ROCKY MOUNTAIN SPOTTED

---

\*PRESENTED AT THE 1986 NIH HONOR AWARDS CEREMONY, MASUR AUDITORIUM, JUNE 16, 1986.

\*\*DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND

FEVER PROVIDED THE KEY FOR FINDING THE CAUSE OF ONE OF THE GREAT PLAGUES OF MANKIND--EPIDEMIC TYPHUS. RICKETTS DIED OF TYPHUS IN 1910, A VICTIM OF THE ORGANISM THAT HE HAD EARLIER DESCRIBED AND THAT SUBSEQUENTLY WAS NAMED FOR HIM--THE RICKETTSIA.

IN 1912 DR. T. B. McCLINTOCK WAS SENT FROM THE HYGIENIC LABORATORY TO MONTANA TO CARRY OUT A PROJECT THAT HAD BEEN PLANNED BY DR. RICKETTS. HE COMPLETED THE PROJECT, BUT CONTRACTED SPOTTED FEVER AND DIED SHORTLY AFTER RETURNING TO WASHINGTON.

A GIANT AMONG THE REMARKABLE MEMBERS OF THE STAFF OF THE HYGIENIC LABORATORY WAS DR. JOSEPH GOLDBERGER. CONSIDERED TO BE ONE OF THE MOST PROMISING OF THE YOUNG MEN CONNECTED WITH THE HYGIENIC LABORATORY, HE WAS PLACED IN CHARGE OF THE PUBLIC HEALTH SERVICE INVESTIGATION OF PELLAGRA, THEN PREVALENT IN THE POVERTY-STRICKEN SOUTH, BUT KNOWN AS A PROBLEM IN 40 STATES AS WELL AS THE DISTRICT OF COLUMBIA. THE PUBLIC HEALTH SERVICE WAS DETERMINED TO MAKE AN ATTACK ON PELLAGRA, THOUGHT BY MOST MEDICAL SCIENTISTS OF THE TIME TO BE CAUSED BY A PARTICULAR ORGANISM. DR. GOLDBERGER ARGUED THAT IF A BACILLUS WERE THE CAUSE, SOME OF THE DOCTORS AND NURSES AND OTHER ATTENDANTS WORKING AROUND THE PELLAGRA PATIENTS DAILY WOULD GET IT TOO. HE POINTED OUT THAT THE ONE DIFFERENCE BETWEEN THE INMATES IN PRISONS AND MENTAL INSTITUTIONS, AND THE PEOPLE WHO CARED FOR THEM WAS THEIR DIET--YET, MANY OF THE INMATES SUFFERED FROM PELLAGRA, THEIR ATTENDANTS DID NOT. DR. GOLDBERGER'S CONFIRMATORY INVESTIGATION WAS A CLASSIC OF EPIDEMIOLOGY. HE WAS A

MASTER OF BOTH OBSERVATION AND EXPERIMENTATION. GOLDBERGER AND HIS ASSOCIATES SHOWED THAT THE POOR, MONOTONOUS DIETS COMMON TO MANY LOW-INCOME PEOPLE--DIETS HIGH IN CARBOHYDRATE AND LOW IN GOOD QUALITY PROTEIN AND FRESH VEGETABLES--INDUCED PELLAGRA WHEN FED TO VOLUNTEER CONVICTS IN A MISSISSIPPI PENITENTIARY. IN OTHER PUBLIC INSTITUTIONS WHERE THE DISEASE OCCURRED, THESE INVESTIGATORS DEMONSTRATED THAT GENEROUS AMOUNTS OF MILK, EGGS, MEAT, BEANS, AND PEAS PREVENTED IT. STILL, PHYSICIANS WHO WERE TREATING PELLAGRA AT THE TIME STRONGLY BELIEVED THAT IT WAS DUE TO AN INFECTIOUS ORGANISM AND WOULD NOT ACCEPT GOLDBERGER'S EVIDENCE.

AS A FINAL PROOF THAT NO INFECTIOUS MECHANISM WAS INVOLVED, GOLDBERGER AND ONE OF HIS COLLABORATORS INJECTED EACH OTHER WITH BLOOD FROM A PELLAGRA PATIENT. LATER GOLDBERGER AND FOUR ASSOCIATES SWALLOWED CAPSULES CONTAINING PATIENTS' WASTES AND SKIN SCRAPINGS, AND GOLDBERGER INJECTED BLOOD FROM A PELLAGROUS WOMAN INTO HIS WIFE, MARY. NONE CONTRACTED THE DISEASE, THOUGH IT IS NOT RECORDED WHAT ADVERSE SYMPTOMS MAY HAVE RESULTED FROM THESE HEROIC EXPERIMENTS.

HE LATER DEVELOPED A TREATMENT USING YEAST IN THE DIET AND SHOWED THAT THE AMINO ACID TRYPTOPHAN WAS CRUCIALLY RELATED TO THE CAUSE OF THE DISEASE. SOON THE B. VITAMIN NICOTINIC ACID, NOW CALLED NIACIN, WAS IDENTIFIED AS A SPECIFIC PELLAGRA PREVENTIVE. THUS THE KEEN INSIGHT, PERSISTENCE AND HEROIC COMMITMENT OF DR. GOLDBERGER AND HIS ASSOCIATES DEFEATED A



WIDESPREAD AND DEVASTATING DISEASE. THERE ARE MANY MORE SUCH  
SAGAS OF HEROISM, DEDICATION AND HIGH ATTAINMENT IN OUR HISTORY,  
AND ONE CAN SAY WITH ASSURANCE THAT SOME ARE TAKING PLACE AT  
THIS TIME, IN THIS PLACE.

I WISH TO EXTEND TO ALL OF TODAY'S HONOREES, THEIR  
FAMILIES, AND THEIR FRIENDS MY HEARTIEST CONGRATULATION FOR THE  
HONOR YOUR ACCOMPLISHMENTS HAVE EARNED.

## REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

Good morning, and thank you Dr. Becker.

Very rarely do we give the buildings of NIH much consideration as entities unto themselves. Building 8, affectionately known as "Old Flat Top" has a rather unique history. When Buildings 4 and 5 were completed in 1941, there was still some money left over. It was decided to construct an additional building with the remaining funds, but no gable was ever put on the three-story structure because more floors were to be added later, hence the "Flat Top." The NIH Alamac recorded that the cornerstone for Building 8 was laid in April of 1945, and original construction costs were \$199,614. There is no completion date listed in the Almanac, which leads me to conclude that Building 8 must hold the title for NIH's slowest building.

It is only 41 years from April 1945 to June of 1986 as we cut the ribbon to mark the completion of Building 8. Turned sideways, the number 8 is the symbol for infinity, which might have been a better designation. Perhaps Dr. Becker's greatest achievement may be as "the man who finished Building 8."

Despite this rather checkered past, some very important work has been done in these long incomplete walls. NIAID had the Laboratory of Parasitic Diseases here, with its insectary where so much important work on malaria took place. As most of you know, a malaria vaccine is now being tested in humans, a direct result of work begun here in Building 8. This was also the site of NIH's first germ-free lab. NCI's Mike Potter did much of his work here with plasmacytoma and murine myeloma. Today that research has seen clinical realization in the development of monoclonal antibodies.

But perhaps Building 8's most famous resident, to date, has been NINCDS' D. Carleton Gajdusek. Carleton moved to this building in 1962. Here in February of 1963 he inoculated a chimpanzee with "Kuru" virus. That chimp went on to manifest the symptoms of the disease, proving that the syndrome found among the New Guinea natives was not a genetic or psychosocial disorder. As we all know, that research ultimately won him the Nobel Prize for identifying the first slow virus. Perhaps it is appropriate that NIH's slowest building should be home to the first slow virus research.

I think this brief listing of Building 8 accomplishments provides a real challenge to the new occupants from NIH's newest old Institute. You now have your chance to make your mark in "Old Flat Top." I am sure under the guidance of Dr. Roth you are up to the test.

---

\*On the Occasion of the Dedication and Ribbon-Cutting of the Newly Renovated Building 8, NIH, on June 19, 1986.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



## REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

On behalf of the NIH, I am very pleased to welcome all of you to the Stone House garden this afternoon. We are especially happy that Counselor Ikeda and his colleagues from the Embassy of Japan are able to be with us, as well as Mr. McPherson, representative from the Department of State. Also with us this afternoon are some of the 300 visiting scientists from Japan currently collaborating with NIH investigators in our intramural laboratories.

We are here today to accept and dedicate this Stone Tower, given to the NIH in honor of Professor Kozo Okamoto of Kinki University, by his friends, colleagues, and students.

Dr. Okamoto has made very special contributions to research related to hypertension, and this Stone Tower will stand to remind us of Professor Okamoto's accomplishments and the contributions of other scientists who based their work on the animal model he developed.

In a broader sense, the Tower will also serve as a symbol of the long-standing and active cooperation in biomedical research between Japanese and American scientists. Since the inception of our visiting scientist program in 1950, more than 1,100 Japanese scientists have come to NIH to share research experiences with our own scientists. The relationship has been strong and steady--in the past 15 years, Japan has been among the top 5 recipients of NIH awards of all categories. This relationship has been exceedingly successful. Studies of the hypertensive rat model; of HTLV-I, the cause of T-cell leukemia; and of familial hypercholesterolemia--which have contributed so much to the advancement of science and health--are but some examples of fruitful sharing between Japanese and U.S. scientists. Moreover, the partnership has been warm and mutually satisfying.

On behalf of the NIH, I am very grateful to receive this splendid Tower, placed here appropriately at the Stone House, NIH's center for international activities.

---

\*On the Occasion of the Dedication of the Japanese Stone Tower at NIH in Honor of Professor Kozo Okamoto of Kinki University on July 2, 1986.

\*\*Director, National Institutes of Health, Bethesda, Maryland.





## REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

On behalf of the NIH, I am very pleased to welcome all of you to the Stone House garden this afternoon. We are especially happy that Counselor Ikeda and his colleagues from the Embassy of Japan are able to be with us, as well as Mr. McPherson, representative from the Department of State. Also with us this afternoon are some of the 300 visiting scientists from Japan currently collaborating with NIH investigators in our intramural laboratories.

We are here today to accept and dedicate this Stone Tower, given to the NIH in honor of Professor Kozo Okamoto of Kinki University, by his friends, colleagues, and students.

Dr. Okamoto has made very special contributions to research related to hypertension, and this Stone Tower will stand to remind us of Professor Okamoto's accomplishments and the contributions of other scientists who based their work on the animal model he developed.

In a broader sense, the Tower will also serve as a symbol of the long-standing and active cooperation in biomedical research between Japanese and American scientists. Since the inception of our visiting scientist program in 1950, more than 1,100 Japanese scientists have come to NIH to share research experiences with our own scientists. The relationship has been strong and steady--in the past 15 years, Japan has been among the top 5 recipients of NIH awards of all categories. This relationship has been exceedingly successful. Studies of the hypertensive rat model; of HTLV-I, the cause of T-cell leukemia; and of familial hypercholesterolemia--which have contributed so much to the advancement of science and health--are but some examples of fruitful sharing between Japanese and U.S. scientists. Moreover, the partnership has been warm and mutually satisfying.

On behalf of the NIH, I am very grateful to receive this splendid Tower, placed here appropriately at the Stone House, NIH's center for international activities.

---

\*On the Occasion of the Dedication of the Japanese Stone Tower at NIH in Honor of Professor Kozo Okamoto of Kinki University on July 2, 1986.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



WELCOMING REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

I am pleased to welcome you to the National Institutes of Health and to the Warren Grant Magnuson Clinical Center. This remarkable institution is dedicated to the challenge and promise of biomedical research. While the hospital and laboratories provide the means for investigation, the professionals who work here are the lifeblood of the research endeavor. And you, as Medical Staff Fellows, are an essential and integral part of our research community. You are a select group--and we welcome you.

You will be taking on the major responsibilities of patient care. As primary physicians you will be responsible for treatment, for managing complications should they arise, and for carrying out the protocols under direction of an established investigator. Here at the Clinical Center you will be heavily involved in biomedical research. As you know, it is a rigorous and demanding pursuit that requires discipline and hard work, but it offers excitement and intellectual challenge. This campus and this Clinical Center will be your laboratory and work place. Some of you will be participating as Dental Staff Fellows engaging in research and treating patients in the Dental Clinic.

As you devote your time to research in the biomedical sciences, you will learn research methods and design and engage in the logical pursuit of scientific problems and the critical interpretation of the results.

Clinical investigation is a vital segment in the progression from basic research to prevention and treatment of disease, and is of fundamental importance to the National Institutes of Health. There is much to be done and we have the tools, the space, and the people to do it. The Clinical Center is the largest research hospital in the world.

---

\*Presented at the orientation of Medical Staff Fellows,  
National Institutes of Health, July 7, 1986.

\*\*Director, National Institutes of Health, Bethesda, Maryland



You are here at a particularly interesting and exciting juncture in medical research--a time when new and powerful techniques are available for the exploration of areas heretofore inaccessible. Key discoveries in molecular biology, genetics and immunology have led to the widespread use of techniques that will enable you to address fundamental questions about the nature of living organisms. Advances made in the past decade are still diffusing into existing fields of investigation.

Opportunities for new achievements in diagnosis, treatment, prevention, and understanding of the physiological processes underlying disease states are made possible by such accomplishments as:

- o Progress in the studies of structural biology. Work on cell membrane and receptor structure and function can lead to design of tailor-made drugs for more effective action.
- o Technological advances in areas such as x-ray crystallography and magnetic resonance imaging provide new opportunities to investigate the structural properties of physiologically active molecules.
- o Important advances in the technique of genetic mapping have been facilitated by the increasing availability of DNA probes.
- o The utility of hybridomas has been extended well beyond basic research. The impact of monoclonal antibody technology is especially strong in the area of in vitro diagnostic products. Other monoclonals under development are aimed at diagnosis of disease in vivo. Using monoclonals for direct treatment lies further in the future.
- o Investigators in the field of neurobiology have recently succeeded in identifying the locations of several of the more than 30,000 genes that control protein production, and have also produced important new evidence regarding the functions of some of these proteins in the transfer of information within the human brain.

These are but a few examples of the types of research in which you will be participating.

The rapid development of science makes it imperative that there be a continuing flow of new investigators educated and trained in the most modern concepts and techniques of research. To assure that scientists are able to recognize the potential clinical value of research findings, the number of medically trained individuals in the research pool must continually be replenished. The Medical Staff Fellowship Program offers young physicians and dentists this opportunity.

The program began in 1958 with the Fellows called "Clinical Associates." It reached its peak in the period between 1965 and 1970 when the Commissioned Officers Residency Deferment Program (CORD) allowed deferment from military service if a physician or dentist entered the Associate Program here at NIH. During these five years, NIH received more than 1,000 applications annually and from 166 to 226 appointments were made each year. In 1970 the CORD program was discontinued and the number of applicants temporarily declined. Since that time there has been a steady increase.

One of the striking features of the Medical Staff Fellowship Program is that it offers an exciting and stimulating medical setting in which free-ranging inquiry devoted to the study of human disease provides a vigorous incentive to remain in the field. Some remain at NIH for lifetime careers of fruitful research. As you progress through your training experience here, you will notice that many of the senior people, some of them your preceptors, were themselves Clinical Associates. My predecessor as NIH Director, Dr. Donald S. Fredrickson, was in the 1953 prototype of the Fellowship Program, and I might add--so was I.

In any case, through the years Medical Staff Fellows have provided much of the impetus to the research conducted here. Whether you stay at NIH or move to another medical center in this country or abroad, you will have the opportunity to influence the course of medical research in the future and your experience at NIH will constitute a significant resource. We are pleased, indeed, that you are joining us and on behalf of the NIH community I am delighted to welcome you.



821

FEDERAL BIOMEDICAL RESEARCH POLICY, 1986\*

by

James B. Wyngaarden, M.D.\*\*

In the course of my remarks today I will address some of the challenges and opportunities that lie ahead for biomedical research, particularly as they involve and affect the National Institutes of Health. In such a discussion one must address current problems and foreseeable difficulties, but at the outset I wish to declare that I continue to be an optimist about the future of the National Institutes of Health. Despite current fiscal pressures it is my conviction that the road ahead for the National Institutes of Health is promising. I base this belief on the commitment of the Federal Government to the support of biomedical research for the improvement of human health--a commitment that is steady and strong in both the executive and legislative branches.

- o The total national expenditures for health research and development during 1985 were estimated at \$13.5 billion. The Federal Government was the source of just over one-half of the total or about \$6.8 billion. The NIH was the source of \$4.8 billion, or over 35 percent of funding for health research and development in the nation. Industries, as a whole, spent about 37 percent or slightly more than the NIH share.
- o This comparative increase in industry's participation in health R&D is recent. Ten years ago industry's expenditures amounted to a substantially smaller share--27 percent.
- o Along with increased expenditures, new kinds of relationships have been established by industrial organizations with some of our finest academic institutions. Ingenious contractual arrangements have been devised to protect the interests of both parties with respect to such essentials as freedom of inquiry and open scientific communication.

---

\*Address presented at the Memorial Sloan Kettering Cancer Center in New York, July 11, 1986.

\*\*Director, National Institutes of Health, Bethesda, Maryland



- o The NIH has a deep and continuing interest in such new partnerships but has not interposed itself in them.

#### NIH Since 1945

- o The NIH shortly will begin observance of its centennial, celebrating "a century of science for health." There are many fascinating stories of human courage and of brilliant scientific achievement in the institution's history. For today's discussion, however, I will confine historical references to budgetary trends and policy developments of the past 40 years.
- o The period since the end of World War II is the era of the modern NIH--the agency as we know it today. Prior to the war, almost all of its research had been in-house. After 1945 the partnerships that had been established with universities, medical schools, hospitals, and other research institutions in the war effort were continued and, in fact, strengthened. Currently about 88 percent of NIH funds are committed to extramural research and training. (Slides 1a, 1b)
- o Every year since 1945, with only a few exceptions, the annual NIH budget has increased. For a part of that time, until 1968, the increases were spectacular. From 1945 to 1968 the budget grew at an astounding average rate of 24 percent per year.

#### Adjusting to Deceleration in Budget Growth

- o By 1970, due largely to the budget stresses of the Vietnam war, the NIH appropriation took a step backward and was more than 16 percent below the 1967 level. Some saw the reduction as the "beginning of the end of Federal support for biomedical research." It was the "end of the beginning"--even so, the NIH budget has not since then been reduced from one year to the next.
- o The growth rate since 1968 has averaged about 2 percent per year in purchasing power. (Slide 2)

- o By 1970 a well-planned initiative led to the "war on cancer" with the President and the Congress vying for the leadership in providing funds and organizational innovations for the conquest of cancer. Between 1971 and 1973 the budget of the National Cancer Institute more than doubled in current dollars. It had tripled by 1975.
- o The National Heart, Lung, and Blood Institute also experienced a period of rapid growth, increasing by 54 percent between 1971 and 1973, and doubling by 1977.
- o The budgets of both NCI and NHLBI grew faster than the total NIH budget during the early and mid '70s. By the end of the decade, however, the growth differentials generally disappeared.
- o Beginning in the early 1970s and continuing to the present, another set of program adjustments has taken place involving shifts among the mechanisms used for funding research. Priority was given to research project grants with a concomitant reduction in budget for research contracts and research training. (Slide 3)

#### Priority for Project Grants and Heightened Competition

- o The total number of project grants supported in 1972 was 10,290, by 1985 the total had grown to 18,219. In this period the average award per project remained virtually unchanged in constant dollars. The average in current dollars, however, increased from \$59,000 in 1972 to \$147,000 in 1985. (Slide 4) Indirect costs, however, took an increasing share of the research award, rising from 21 percent in 1972 to 31.3 percent in 1985. (Slide 5) Consequently, the real dollars available per project for direct costs were reduced, or at best, constant.
- o The progress of science has resulted in an increased number of grant proposals. A total of 18,675 competing research grant applications were reviewed in 1985. In 1976 the total was 10,050, and in 1971 less than 8,000. (Slide 6)

- o We have become increasingly concerned about maintaining a relatively stable and predictable level of new and competing renewal grants. The number of competing awards fluctuated widely over the past decade, from a low of 3,464 in FY 1976 to a high of 6,247 in FY 1985.
- o We made it a major goal of our original "stabilization initiative" to fund at least 5,000 new and competing renewal grants each year atop the moral commitments of some 11,000 continuation grants. In all but 3 of the past 10 years we have awarded at least 5,000 new and competing renewal grants. Budget limitations, however, have precluded a comparable degree of stability for other research and training programs of the NIH.
- o However, in spite of the progressive annual shift of funds into research project grants, the number of applications has grown faster than resources.

In 1976 we could fund about 48 percent of grants eligible for award, but in 1984, 1985 and 1986 we were only able to fund about 37 percent. As would be predicted, the paylines are progressively lower.  
(Slides 7, 8)

Side Effects of Increased Competition - Stresses on the  
Peer Review and Awards System

- o Another result of fiscal constraints plus increased competition is the increasing frequency with which grant proposals are being resubmitted after unsuccessful competitive review. In 1965, 6 percent of applications reviewed were resubmissions--in 1975, 15 percent were resubmissions, and by 1985 the proportion of resubmissions was about 25 percent of all applications. As might be expected, resubmitted applications enjoy a higher success rate than initial proposals, reflecting heightened influence of the study section on the form and substance of grant applications.
- o In response to the tougher competition and the widespread perception that study sections often look for minor flaws or omissions in

proposals under review and that small factors shift priority scores, applicants tend to overdocument. As a result, the workload for both the applicant and the study section is greatly increased.

- o Although fiscal constraints are responsible for much of the difficulty experienced by the research community, certain attributes of the current extramural award system may be more burdensome than necessary for the investigator, the grantee institution, and the NIH peer review system. In order to increase productivity with the resources available to us, we have instituted several changes in the review and award process.
- o In our judgment one of the factors that is contributing needlessly to the workload of both the grant applicant and the NIH peer review system is the excessive complexity and sheer bulk of the research grant application. In addition to proposing page limitations for grant application, we have taken other steps to reduce the reviewing time for study section's members as well as preparation time for the applicant.

#### FIRST and MERIT Awards

- o We have observed that when the award rate falls the percentage of successful first-time applicants also falls. It is essential to the vitality of the scientific enterprise and to the morale of the scientific community that young scientists be encouraged. We recently announced a new program called FIRST awards (First Independent Research Since Training)--a modification of the R-23s which lengthens the awards from 3 to 5 years and the total to \$350,000 of direct costs for the 5 years. This should obviate the need for too early reapplication for investigators who encounter difficulties in the first 18 months of their grants. It will, we believe, encourage more creative and less defensive research.
- o Further, we have expanded the number and types of longer term support for outstanding mid-career scientists through a new program called



MERIT awards (Method for Extending Research in Time). This program will involve facilitated extensions of 5-year awards for an additional 3 to 5 years on the basis of a detailed progress report, rather than through reapplication. (The extension will be tallied as a competing renewal.)

- o We believe that a greater number of longer grants to both first-time and established investigators represents an efficient and prudent investment of public funds. However, the budgetary implications in the fourth and fifth years and beyond are substantial, and in the absence of major funding increases could reduce the number on new and competing renewal grants we would be able to make in future years.

#### Research Training and Career Development

- o There are two general categories of NIH training programs--those funded through National Research Service Awards (NRSA) and those encompassed in the more advanced career development series.
- o Individual fellowships are awarded through national competition under the NRSA. Institutional awards under the NRSA program permit institutional selection of trainees at both the predoctoral and postdoctoral level. The medical science training program, supported through institutions within the NRSA program, is considered to be one of the most successful in an area critically important to the future.
- o The 1985 appropriation permitted a substantial increase of stipends in postdoctoral categories making the income for clinical postdoctoral fellows and trainees more compatible with that of house staff. Equity was maintained for the Ph.D. who, after two years of postdoctoral training, is contributing in an important way to research activity. Postdoctoral stipends were increased so that with funds for tuition and other expenses, our total outlay per student per year became essentially the same as that offered by the National Science Foundation.

- o Opportunities for advanced research preparation are offered through the NIH Research Career Development Program (K Series). The oldest of these is the Research Career Development Award (RCDA), solely for salary and fringe benefits. More than 80 percent of those who have received RCDAs now have research project grants. Other K Series awards include the Academic Investigator Award, the Clinical Investigator Award, the Mid Career Development Award, and the Physician/Scientist award. These awards provide a salary of up to \$40,000 plus applicable fringe benefits. The actual salary is intended to be comparable to that of others at the same institution at the same level of training and experience.
- o The 1985 appropriation provided over \$217 million for 10,623 NRSA fellows and trainees. The 1986 appropriation (after Gramm-Rudman) is for \$209 million and will support 9,947 NRSA fellows and trainees.

Our budget for career development programs in 1985 was over \$76 million, supporting 1,318 awards. The 1986 budget for career awards is about \$100,000 lower than last year's and provides for 44 fewer awards.

#### Instrumentation, Facilities and Laboratory Animals

- o Over the past decade increasing concerns have been expressed regarding obsolescence of research instrumentation and facilities in the nation's research institutions. A study on instrumentation jointly funded by the National Science Foundation and the NIH was completed last year. The report showed a national need for newer equipment in many laboratories, particularly public institutions. The outstanding need seems to center on relatively low cost instruments in the \$10,000 to \$75,000 range, perhaps reflecting some degree of success in warding off critical needs for large instruments through ongoing NIH programs for sharing such instruments.
- o For a number of years the condition of academic research facilities has steadily deteriorated. Federal support in this area has been

limited and diminishing. The extent of the need for Federal support of health-related research facilities is difficult to ascertain since no comprehensive assessment of this need has been made since 1968.

- o During the past century virtually every major development in biomedical research has depended at some point upon the use of animals. A small but determined segment of society is opposed to the use of animals in research, and they are bringing increasing pressure on scientists, physicians and many institutions staging sit-ins, demonstrations, as well as vandalism, break-ins and bomb threats against investigators and others associated with studies requiring animals.

There is a critical need to develop better understanding among the general public, the mass media and elected officials on the scientific imperatives of using animals in research. The scientific community must recognize its vulnerability in the highly charged emotional climate that surrounds the laboratory animal issue.

#### Appropriations for FY 1986 and Fy 1987

- o Appropriations subcommittees of both the House and Senate are continuing to consider the President's budget proposals for the NIH for 1987. If we can judge by past performance, the Congress will make a number of changes in the proposed distribution of funds and is likely to increase the support for certain programs. The final outcome, however, is unusually difficult to predict because of the uncertainties surrounding the application of anti-deficit measures, particularly Gramm-Rudman.

Although the Supreme Court decision announced last Monday negates the automatic feature of Gramm-Rudman, the fall-back provisions in the Act established a mechanism for sweeping sequestration of appropriated funds. The Federal deficit is being taken seriously by all concerned and the biomedical research budget is not considered to be exempt from across-the-board cuts. Thus, not only is the 1987 budget

uncertain--we have no absolute fix on the final 1986 total for NIH even though we are more than three-quarters of the way through the fiscal year.

- o The original 1986 appropriation for NIH was about \$5.5 billion. This amount was reduced by \$236.2 million under Gramm-Rudman sequestration. The reduction was applied uniformly against the appropriation of each institute and division, as well as against each research mechanism at the NIH aggregate level, and each identified program or activity. To apply a reduction in such a way was not a simple problem in that it involved a three-dimensional matrix.

Special problems arose in applying the reduction to certain units because of the nature of their budgets. For example, the largest element, by far, of the intramural program is salaries. Next is the cost of operating the "hospital"--the Clinical Center. Short of total disruption it is not possible to make a sharp and sudden reduction in personnel or hospital operating costs. Consequently, a 4.3 percent reduction in total support for such programs quickly translates into a 42 percent reduction in necessary supplies and purchases for intramural programs. I suspect that the problems encountered in the extramural world are similar.

- o The Gramm-Rudman reductions, together with a proposed change in the budgeting procedure for AIDS research, bring the FY 1986 budget to \$5.14 billion.

The President's request for comparable purposes for FY 1987 is just over \$4.9 billion. This is almost a 4 percent decrease from the adjusted 1986 budget and 10 percent down from the original 1986 appropriation.

- o The proposed 1987 budget provides for the new stabilization strategy of 18,000 total grants. Allowing for continuing grants, this would permit approximately 5,100 new and competing renewal grants, but it would be necessary to reduce their amounts by an average of 12 to 15



percent from the study section recommended level. Such reductions would be made on an individual basis, and would vary from institute to institute. (In this context it would be difficult to make any headway in repairing the instrument deficit, for example.)

In the FY 1987 budget, request is made for \$198.2 million for training for the support of about 9,250 trainees, a reduction of 700 from the level proposed for 1986 and of 1,374 from the 1985 level.

Other extramural mechanisms would be maintained at approximately their FY 1986 funding levels. Two exceptions are the Biomedical Research Support Grant (BRSRG) Program and the Extramural Facilities Construction Programs, both of which are proposed for elimination in FY 1987--a step made necessary by our continued emphasis on investigator-initiated research project grants as the most appropriate form of support, and in the face of growing concern over the total budget.

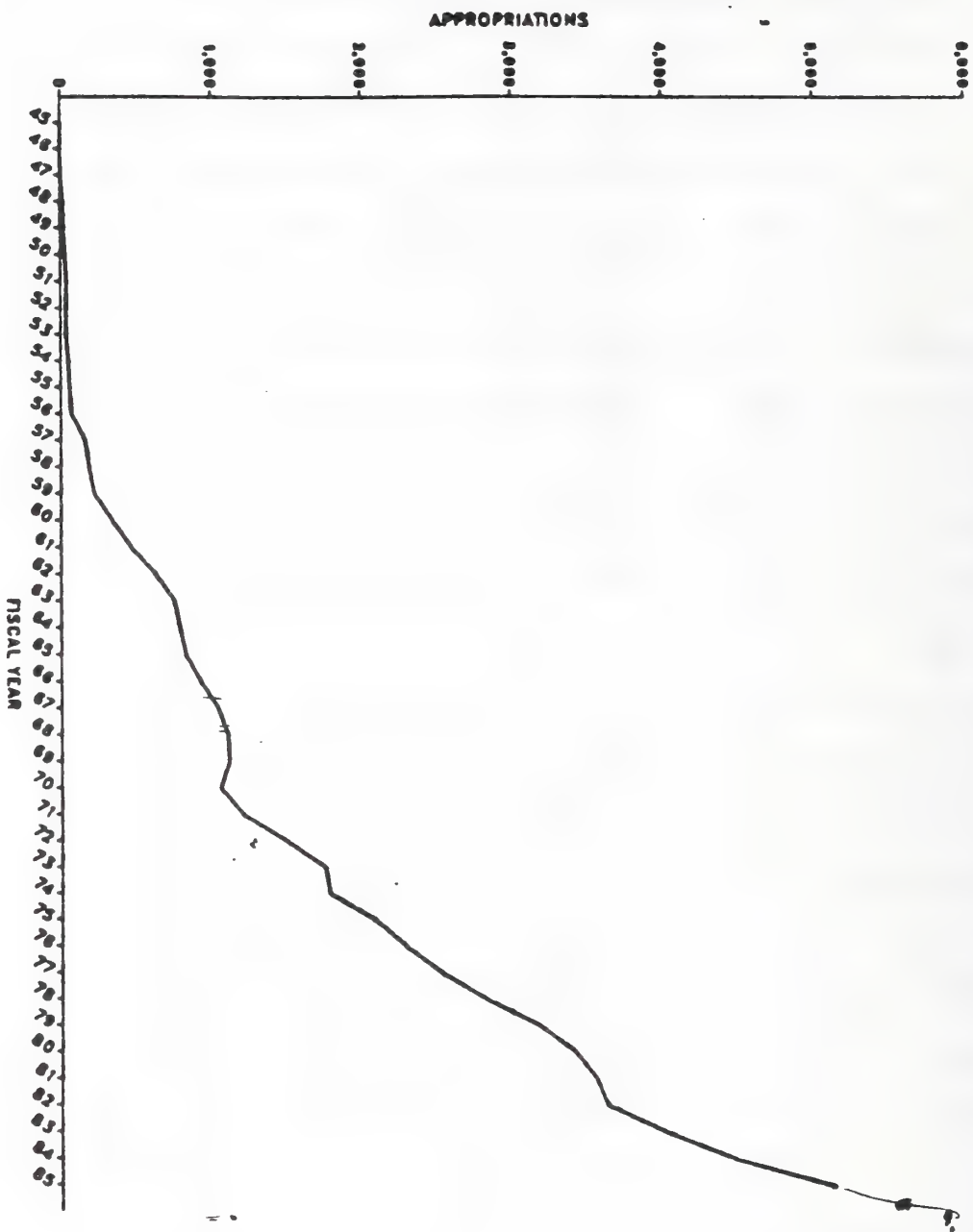
A new method of reimbursing grantees for the indirect cost portion of NIH grant awards was assumed with the President's 1987 budget for NIH. The new policy would set a national maximum limit for academic grantees on the reimbursement rate for the administrative overhead costs. Beginning in FY 1987 the new policy would have capped reimbursement for such administrative costs at 20 percent of the grant's direct costs as compared with the current average of 26 percent for this cost element. The new policy was expected to reduce indirect costs by an estimated \$85 million. To date, however, Congress has rejected this proposed policy and, as a result, OMB is currently exploring alternative proposals to restrain the growth of indirect costs.

- o At the beginning of this discussion I told of my optimism about the future of the National Institutes of Health, and spoke of the commitment to biomedical research of both the legislative and executive branches of the Federal Government. In addition to these champions within the Government, we have many strong advocates outside the Government who act on their conviction of the long-term value of research.

Even the Heritage Foundation, not noted for encouraging Federal expenditures, sounded the same fundamental note that has motivated the establishment and growth of NIH. In a proposal by the staff of the Heritage Foundation for the FY 1987 Federal budget, titled "Slashing the Deficit," the programs of many agencies were examined in detail. Before adding a cautionary note as to how NIH might allocate funds more judiciously, the Foundation staff commented, "Basic biomedical research is one of the few activities funded through Washington which is appropriately a Federal responsibility." The writer continued, "Historically, the benefits of such research have outstripped the taxpayers' cost." I could not have said it better.

I will be happy to respond to any questions you may wish to ask.

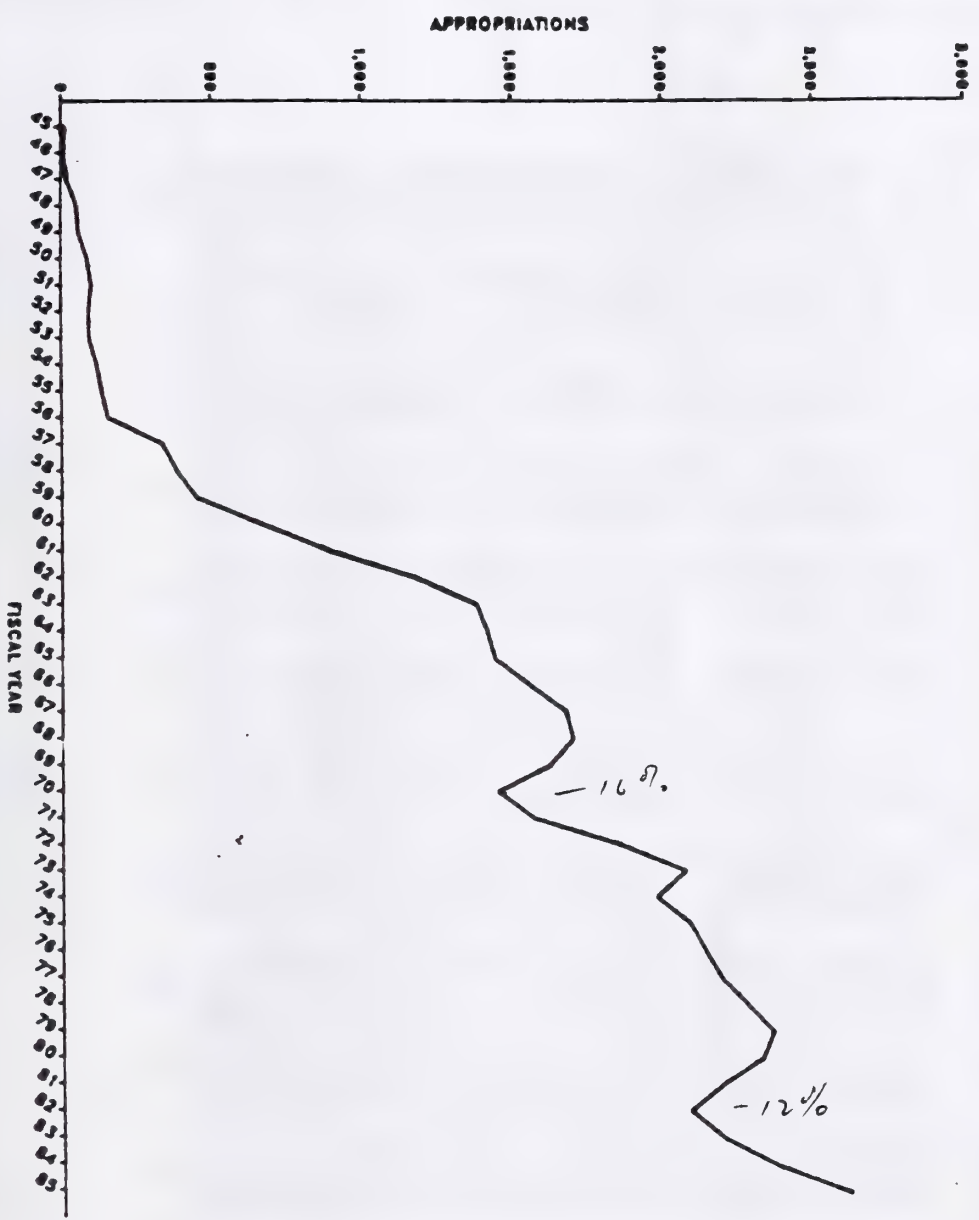
# Total NIH Appropriations in Current Dollars, FY 1945-85 Excluding Programs Transferred Out (Dollars in Millions)



NOTES: TO excluded, 1985 data preliminary.

PAB/DPA/OPPE/OD, April 1985

# Total NIH Appropriations in Constant (1975) Dollars, FY 1945-85 Excluding Programs Transferred Out (Dollars in Millions)



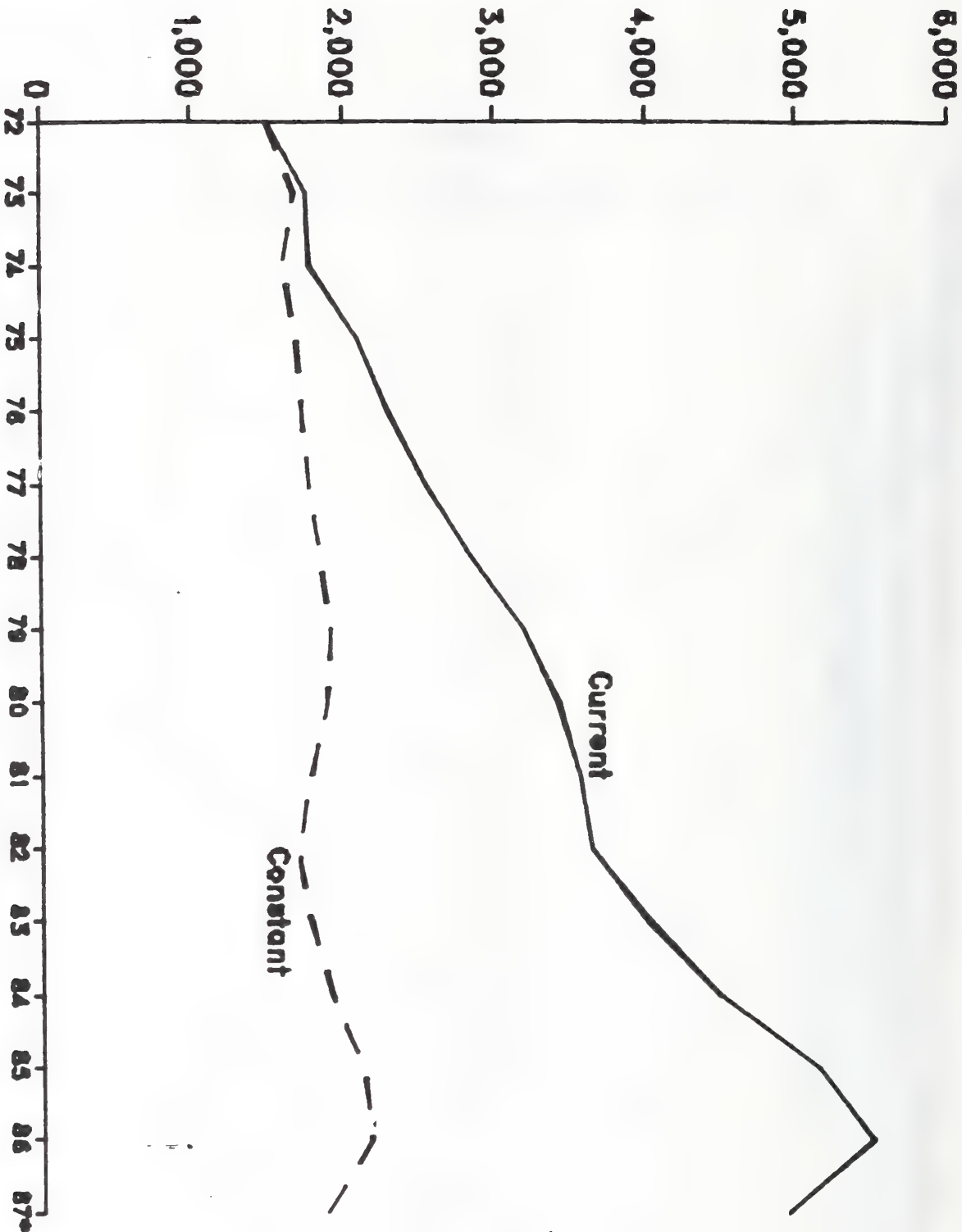
NOTES: Constant dollar conversion uses BRDPI, TQ excluded. 1985 data preliminary.

PAB/DPA/OPPE/00, April 1985



(1972=100)

Dollars in Millions



Fiscal Year

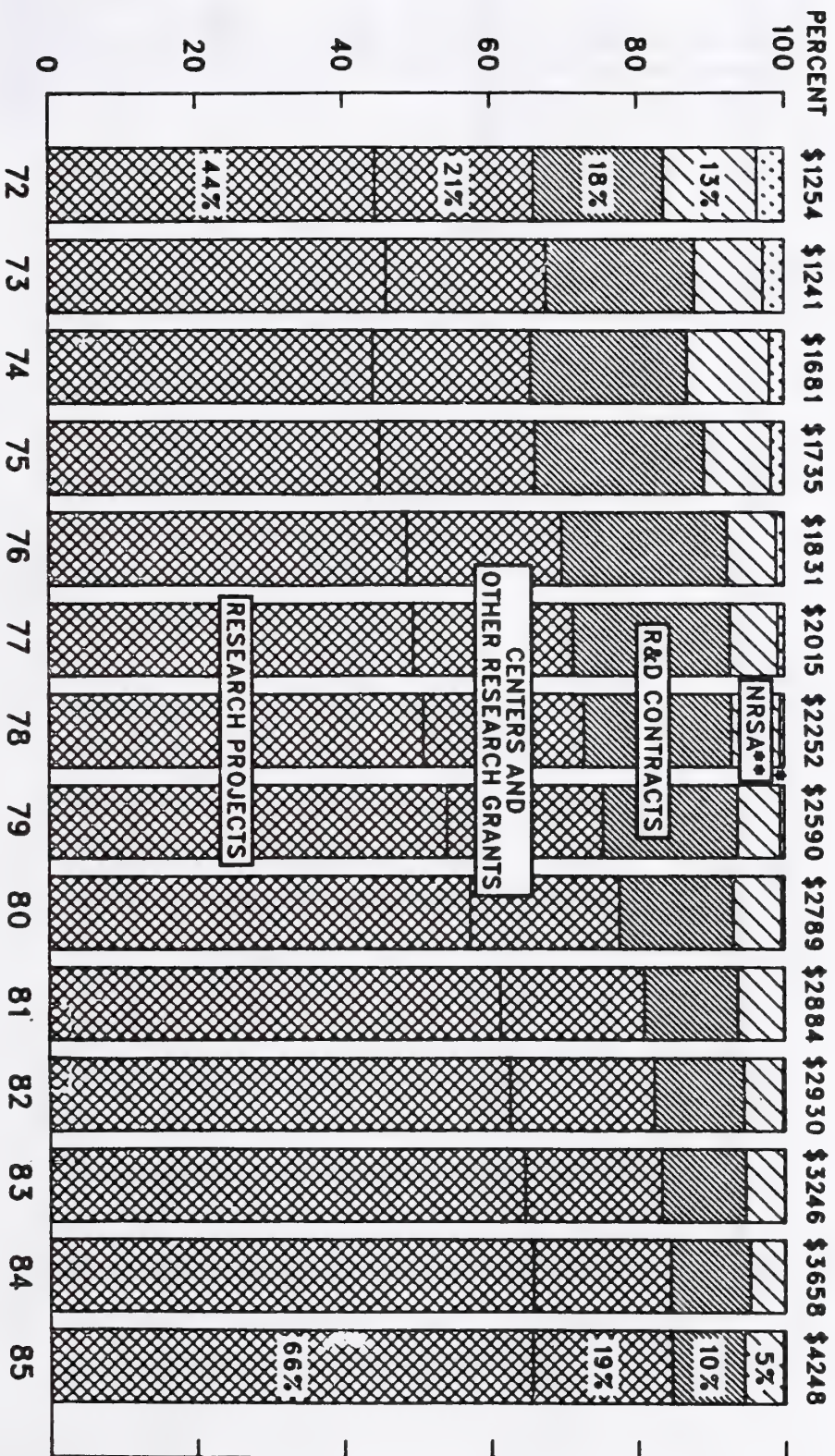
Constant

Current

estima

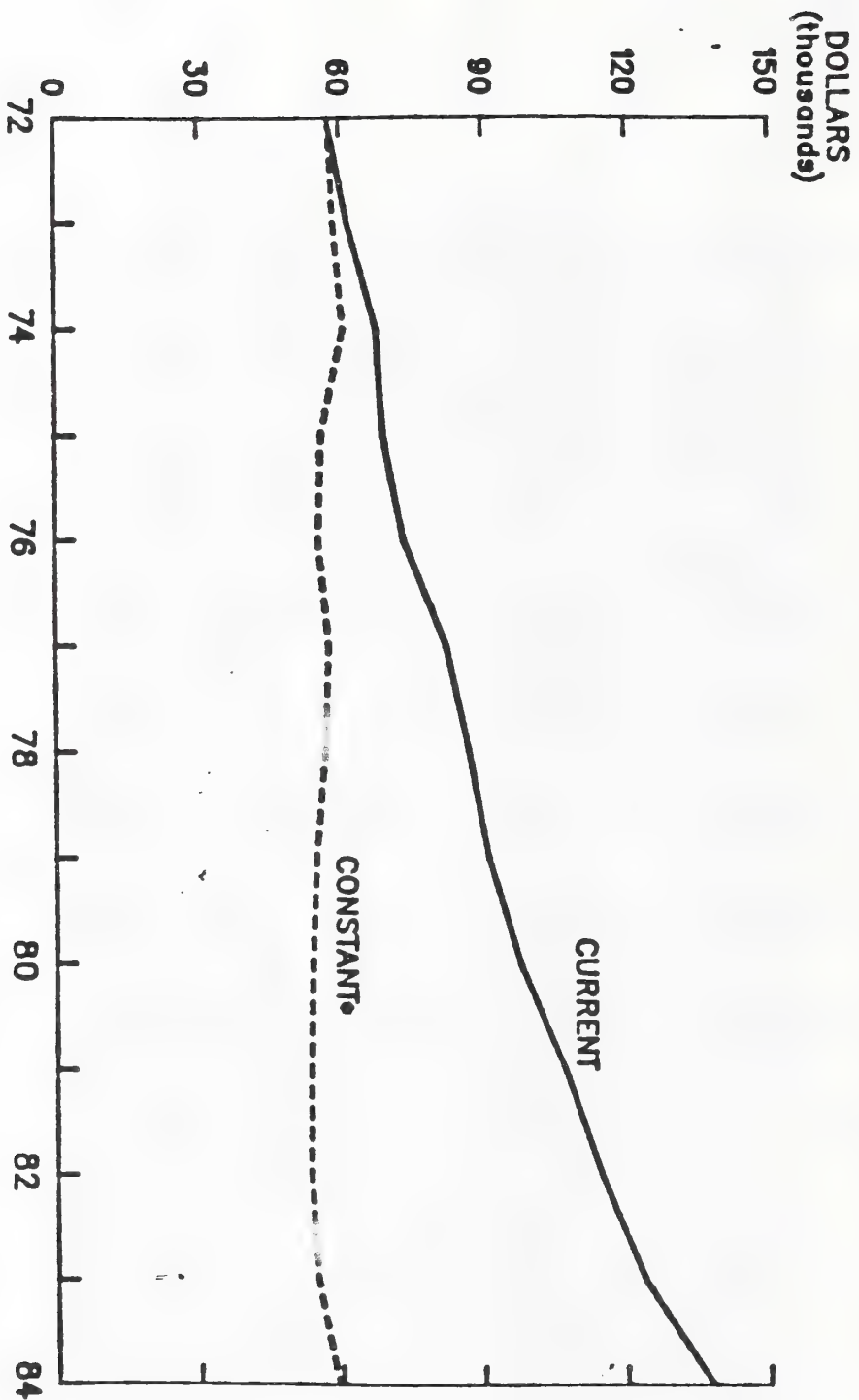
# ALLOCATION OF NIH EXTRAMURAL AWARDS BY ACTIVITY, FISCAL YEARS 1972-1985 PERCENT OF AMOUNT AWARDED (CURRENT DOLLARS IN MILLIONS)

3



NOTE: EXCLUDES TO. \*INCLUDES CONSTRUCTION AND MEDICAL LIBRARY GRANTS. \*\*INCLUDES PRE-NRSA TRAINING.  
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

# AVERAGE DOLLARS FOR NIH RESEARCH PROJECT GRANTS FISCAL YEARS 1972-1984

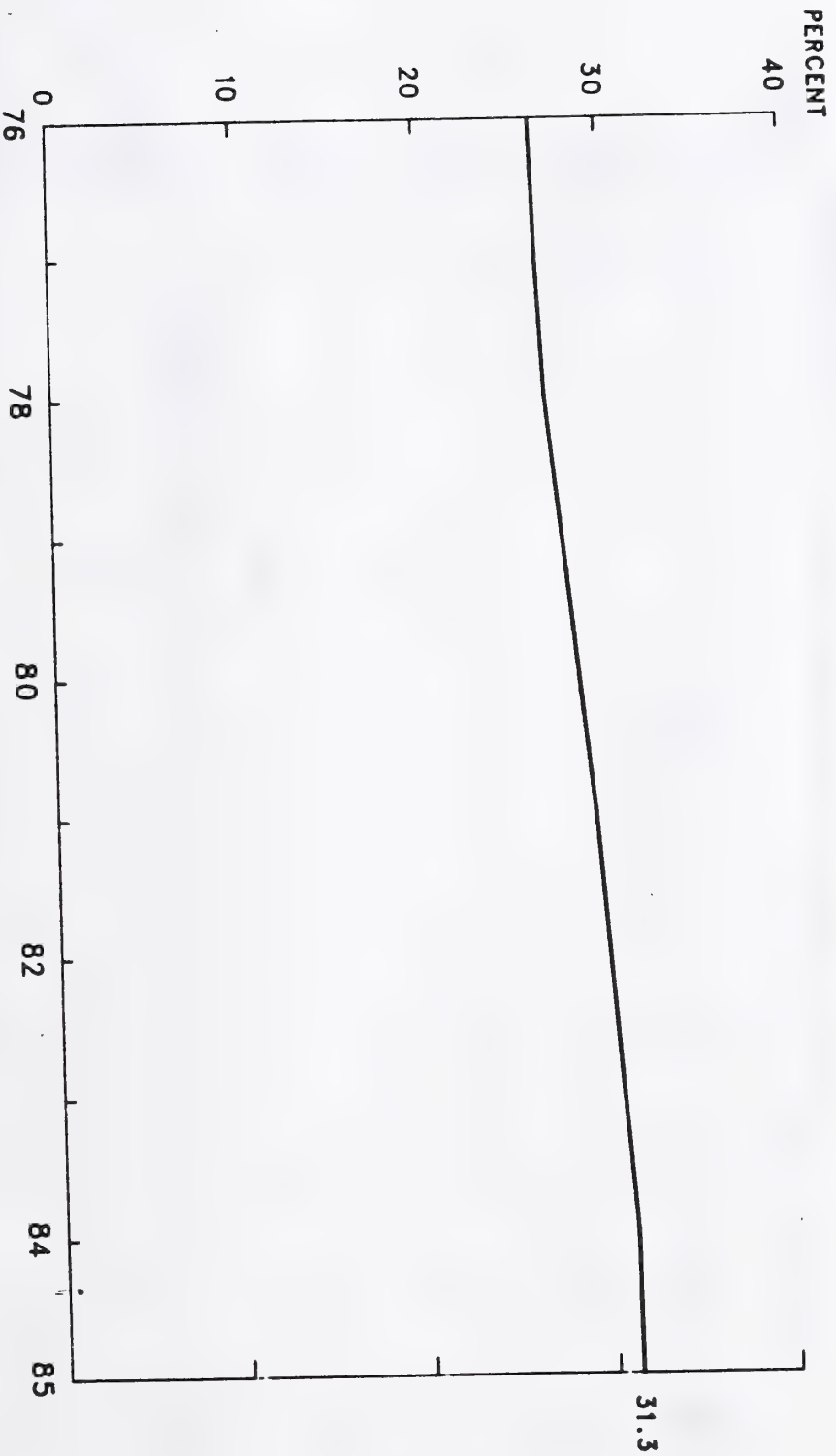


BASED ON BIOLOGICAL AND PRICE INDEX 1972-100.  
SOURCE: NIH, DRE, STATISTICS AND ANALYSIS BRANCH

FIG  
6/14/85

INDIRECT COST PROPORTION OF TOTAL COST FOR NIH RESEARCH GRANTS  
FISCAL YEARS 1976-1985

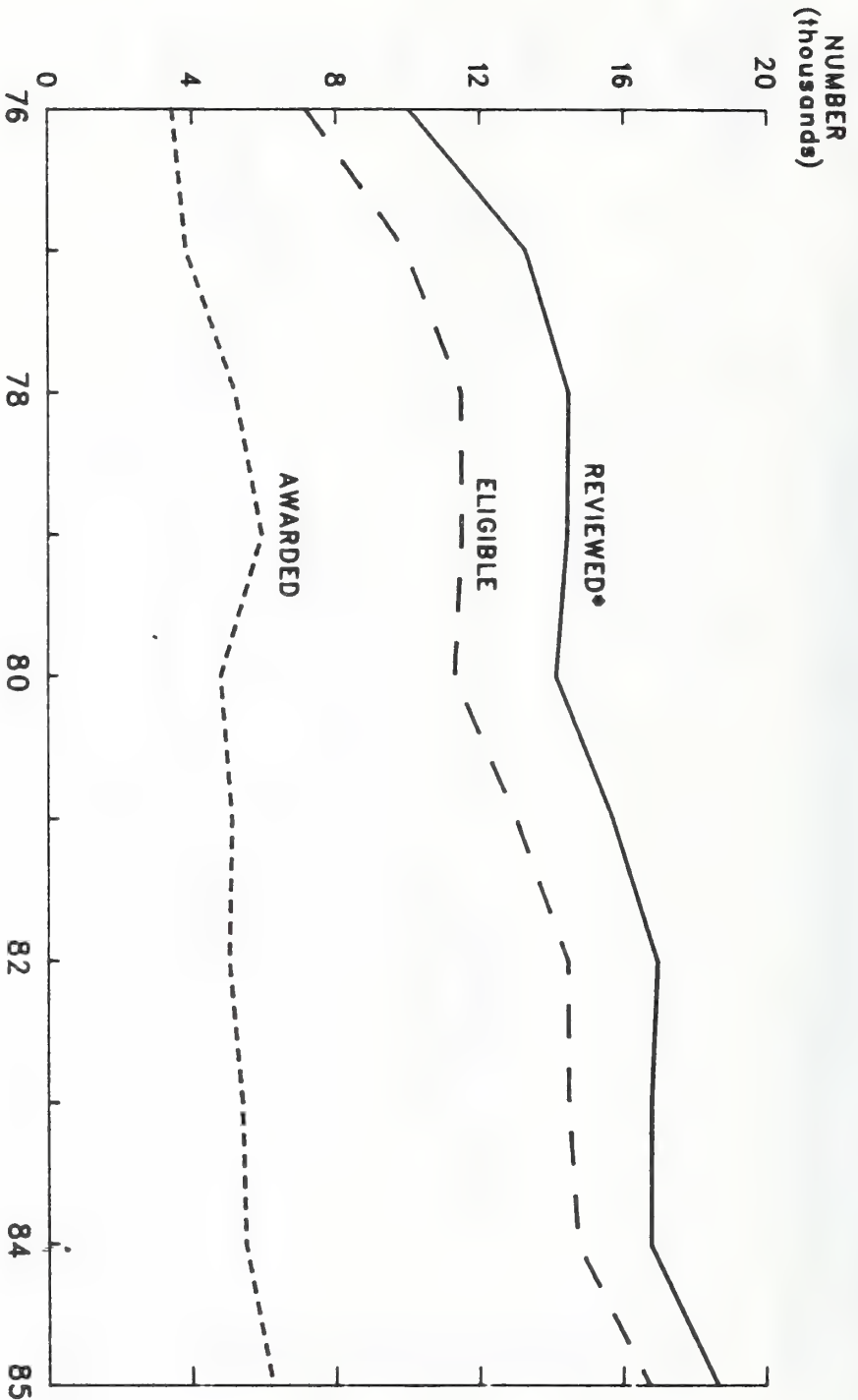
5



NOTE: EXCLUDES CONFERENCE AND NCI EDUCATION GRANTS, BRD, BRS, RCP AWARDS, AND MINORITY STUDENT APPRENTICE PROGRAMS. EXCLUDES THE TQ. SEE TECHNICAL NOTE ON PAGE III FOR ACTIVITY COVERAGE.  
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

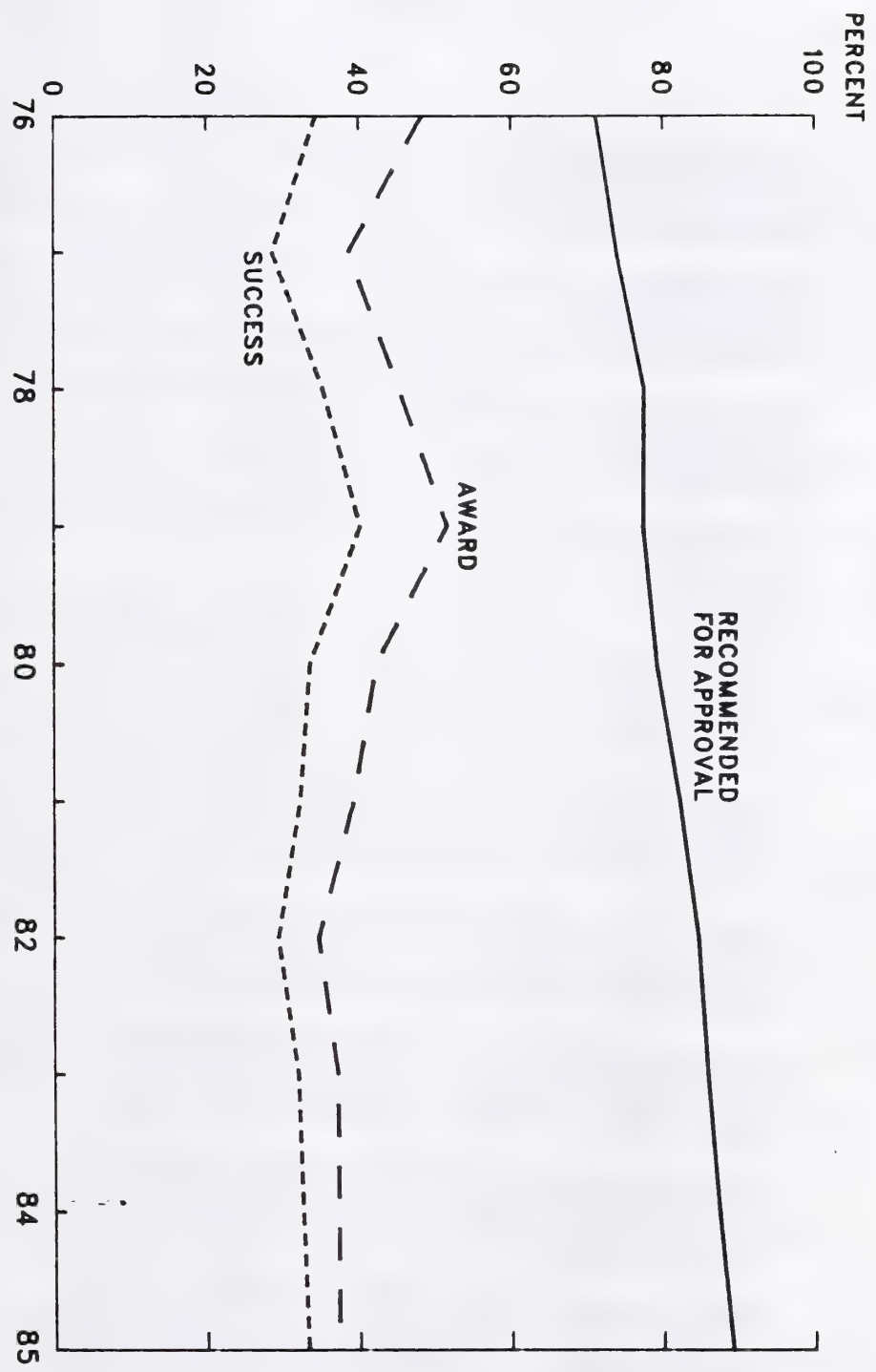


NUMBER OF NIH COMPETING RESEARCH PROJECT APPLICATIONS  
REVIEWED, ELIGIBLE AND AWARDED, FISCAL YEARS 1976-1985



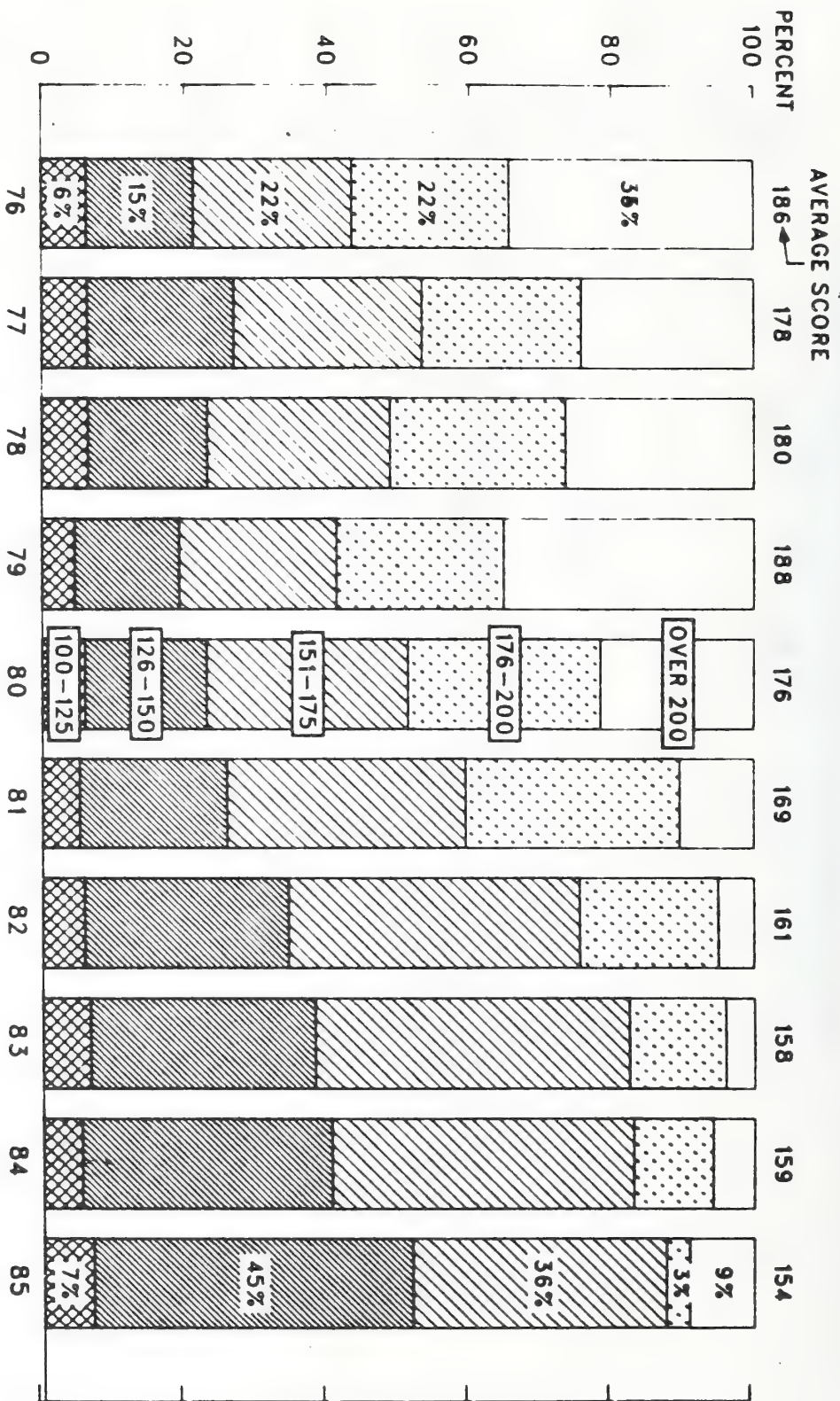
NOTE: EXCLUDES TQ. SEE TECHNICAL NOTE ON PAGE III FOR ACTIVITY COVERAGE AND PROCEDURES.  
\*REPORTING YEAR.  
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

COUNCIL RECOMMENDED FOR APPROVAL, AWARD, AND SUCCESS RATES  
 FOR NUMBER OF NIH RESEARCH PROJECT APPLICATIONS  
 FISCAL YEARS 1976-1985



NOTE: EXCLUDES TQ. SEE TECHNICAL NOTE ON PAGE III FOR ACTIVITY COVERAGE.  
 SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

DISTRIBUTION OF NUMBER OF NIH COMPETING RESEARCH PROJECTS AWARDED  
BY PRIORITY SCORE GROUP, FISCAL YEARS 1976-1985



NOTE: BASED ON ACTUAL SCORES. EXCLUDES TQ.  
SEE TECHNICAL NOTE ON PAGE III FOR ACTIVITY COVERAGE.  
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

## ALTERNATIVE USES OF FUNDS AND PERSONNEL

JAMES B. WYNGAARDEN, M.D.  
DIRECTOR, NIH

AS HAS BEEN STATED REPEATEDLY TODAY AND ON A NUMBER OF OCCASIONS PREVIOUSLY, THE PROPOSAL TO CHARACTERIZE FULLY THE HUMAN GENOME HAS CAPTURED THE IMAGINATION OF A LARGE NUMBER OF EXCELLENT SCIENTISTS AS WELL AS MUCH OF THE PRESS. THE NUMBER OF GATHERINGS AT WHICH DISCUSSIONS ON THIS SUBJECT HAVE BEEN HELD HAS INCREASED RAPIDLY, AND IT MIGHT APPEAR THAT THE PROJECT IS TAKING ON A LIFE OF ITS OWN. THUS, I BELIEVE IT IS USEFUL TO STEP BACK AND SEEK A PERSPECTIVE REGARDING THIS SUBJECT.

FIRST AND FOREMOST MUST BE THE CLEAR STATEMENT THAT WE WOULD NOT BE ABLE EVEN TO THINK ABOUT APPROACHING THIS PROJECT IF IT WERE NOT FOR THE ENORMOUS BREADTH AND DEPTH OF OUR KNOWLEDGE OF GENETICS AND MOLECULAR BIOLOGY AND THE SOPHISTICATION OF NEW TECHNOLOGIES. ALL OF THIS, OF COURSE, HAS COME ABOUT BECAUSE OF THE VERY GREAT SUPPORT PROVIDED BY NIH (AND INDEED NSF ALSO) FOR THE SCIENTIFIC BASE. THE NIH SUPPORT FOR RESEARCH WHICH CAN BE PROPERLY CALLED "GENETICS" IN THE BROADEST SENSE OF THE TERM IS ABOUT ONE-HALF A BILLION DOLLARS PER YEAR. IN FISCAL YEAR 1985, RESEARCH IN HUMAN GENETIC DISEASES WAS ABOUT \$213 MILLION. IN THE NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES ALONE, THERE IS SUPPORT FOR ABOUT \$20 MILLION OF RESEARCH GRANTS IN AREAS INVOLVING MAPPING, GENOME SEQUENCING, LINKAGE STUDIES, AND DNA POLYMORPHISMS. IN ADDITION, A NUMBER OF RESEARCH RESOURCES ARE PROVIDED TO FACILITATE THESE ENDEAVORS:



1. THE HUMAN GENETIC MUTANT CELL REPOSITORY: ESTABLISHED IN 1972, THE NUMBER OF CELL LINES IN THE REPOSITORY HAS GROWN GREATLY AND NOW IS AT 4,000, FROM A VARIETY OF CELL TYPES DERIVED FROM MORE THAN 200 HUMAN GENETIC DISORDERS. THE COST OF MAINTAINING THIS CELL BANK IS JUST SHORT OF \$1 MILLION A YEAR.
  
2. GENBANK<sup>®</sup>: THIS CONTRACT WAS ESTABLISHED IN 1982 AND HAS MADE 44 RELEASES OF DNA SEQUENCE INFORMATION TOTALING OVER 8 MILLION BASE PAIRS. EIGHTY-TWO PERCENT OF ALL SEQUENCES PUBLISHED SINCE 1981 ARE NOW IN GENBANK<sup>®</sup>. ALTHOUGH THIS IS AN INTERAGENCY PROJECT INVOLVING THE DEPARTMENT OF ENERGY (DOE), NSF, AND THE COMPUTERIZED COMMUNICATION NETWORK (DARPA) OF THE DEFENSE DEPARTMENT, THE PRIMARY SUPPORT COMES FROM NIH THROUGH A CONTRACT TO BOLT, BERANEK AND NEWMAN, WHICH IN TURN HAS A SUBCONTRACT WITH THE LOS ALAMOS NATIONAL LABORATORY.

AS OF MID-JUNE, GENBANK<sup>®</sup> HAS OVER 1.2 MILLION BASE PAIRS OF SEQUENCES OF HUMAN DNA. OF GREAT IMPORTANCE IS THE FACT THAT GENBANK<sup>®</sup> IS A TRUE COLLABORATIVE EFFORT WITH THE EUROPEAN MOLECULAR BIOLOGY LABORATORY, THROUGH WHICH DATA ARE EXCHANGED. APPROPRIATE PROCEDURES ARE DEVELOPED. CLEARLY THESE NUCLEIC ACID SEQUENCE DATA BANKS, EACH OF WHICH CURRENTLY COSTS IN EXCESS OF \$700,000 PER YEAR, ARE CENTRAL TO ANY EFFORTS TO TOTALLY MAP OR TO SEQUENCE THE HUMAN GENOME. INDEED PLANS ARE NOW UNDERWAY BETWEEN THE EUROPEAN GROUP AND THE AMERICAN GROUP TO DEVELOP THE NEXT

GENERATION OF METHODOLOGY TO ENABLE THEM TO KEEP UP WITH THE GREAT INFLUX OF DATA THAT SURELY WILL CONTINUE AND THAT MAY WELL BE ENORMOUS IF THE SEQUENCING PROJECT IS UNDERTAKEN IN A SYSTEMATIC FASHION.

3. BIONET: COMPLEMENTARY TO GENBANK<sup>®</sup> IS BIONET, AT THE INTELLIGENETICS DIVISION OF INTELICORP, PALO ALTO, CALIFORNIA. IT WAS STARTED IN 1984.

THE BIONET RESOURCE WAS DEVELOPED:

- ° TO PROVIDE COMPUTATIONAL ASSISTANCE IN DATA ANALYSIS AND PROBLEM SOLVING TO MOLECULAR BIOLOGISTS AND RESEARCHERS IN RELATED FIELDS.
- ° TO SERVE AS A FOCUS FOR DEVELOPMENT AND SHARING OF NEW SOFTWARE.
- ° TO PROMOTE RAPID SHARING OF INFORMATION AND COLLABORATION AMONG A NATIONAL COMMUNITY OF SCIENTISTS.

IT CONSISTS OF A DATABASE LIBRARY INCLUDING GENBANK<sup>®</sup>, THE EUROPEAN MOLECULAR BIOLOGY LABORATORY (EMBL) DATABASE, THE NATIONAL BIOMEDICAL RESEARCH FOUNDATION (NBRF) LIBRARY OF PROTEIN SEQUENCES, VECTORBANK<sup>™</sup>, AND THE RESTRICTION ENZYME DATABASE FROM COLD SPRING HARBOR.

AT PRESENT ALL THE MAPPED HUMAN SEQUENCES THAT WERE KNOWN AT THE TIME OF THE 8TH HUMAN GENETIC MAPPING CONFERENCE (HMG-8) ARE INCLUDED.

4. THE REPOSITORY OF HUMAN DNA PROBES AT THE AMERICAN TYPE CULTURE COLLECTION IS A 5-YEAR CONTRACT COSTING \$1.5 MILLION IN TOTAL. IT STORES AND DISTRIBUTES CHROMOSOME AND GENE SPECIFIC LIBRARIES AS WELL AS NEW PROBES AS THESE ARE DISCOVERED.

IN ADDITION, THERE ARE A NUMBER OF SMALLER, MORE SPECIALIZED RESOURCES AND RESEARCH EFFORTS FOR THE CHARACTERIZATION OF THE HUMAN GENOME.

WHAT DOES ALL THIS MEAN?

CLEARLY, IT MEANS THAT NIH HAS BEEN VERY ACTIVE IN PROMOTING RESEARCH AS WELL AS NEEDED FACILITIES IN THE AREA OF GENETICS; IN PARTICULAR, HUMAN GENETICS. IT ALSO MEANS THAT WE HAVE SUPPORTED MORE IN THE AREAS OF MAPPING AND SEQUENCING THAN YOU MIGHT HAVE THOUGHT, THAT WE HAVE HAD CLOSE LINKS WITH THE EUROPEAN COMMUNITY, AND THAT WE ARE CONTINUOUSLY PROVIDING RESOURCES TO FACILITATE BIOMEDICAL RESEARCH. IT MUST ALSO BE EMPHASIZED THAT ALL OF THIS COSTS A GREAT DEAL OF MONEY, THAT CRUCIAL DECISIONS HAVE TO BE MADE REGARDING THE BALANCE BETWEEN SUPPORT OF RESEARCH AND OF RESEARCH FACILITIES, AND BETWEEN THE NEED FOR ONE RESOURCE OR FOR ANOTHER. AND IT MEANS THAT WE MUST THINK ABOUT ANOTHER RESOURCE WHICH NO ONE HAS YET MENTIONED --RESEARCH MANPOWER. AS THE NATIONAL ACADEMY OF SCIENCES COMMITTEE ON RESEARCH MANPOWER NEEDS HAS REPORTED, THE NUMBER OF PERSONS BEING SUPPORTED FOR FORMAL RESEARCH TRAINING,

PARTICULARLY AT THE PREDOCTORAL LEVEL, HAS BEEN STEADILY FALLING OVER THE LAST FEW YEARS AND IS NOW ABOUT 700 BELOW THE LEVEL THAT THE COMMITTEE HAS RECOMMENDED. I HAVE HEARD THAT GETTING GOOD POSTDOCTORAL MOLECULAR BIOLOGISTS IS VERY DIFFICULT. HIGHLY SKILLED PHYSICIAN-RESEARCHERS ARE STILL FAR TOO FEW. SURELY, IF WE ARE TO HAVE AS CONTINUOUS AND GREAT AN IMPACT ON BIOMEDICAL SCIENTIFIC PROGRESS IN THE FIRST HALF OF THE 21ST CENTURY AS WE HAVE HAD IN THE LAST HALF OF THE 20TH, WE MUST HAVE APPROPRIATE NUMBERS OF HIGHLY SKILLED, HIGHLY TRAINED, CREATIVE SCIENTISTS. AND IF WE WISH TO HARNESS THEIR CREATIVE TALENTS, WE MUST HAVE APPROPRIATE FUNDS FOR THEIR RESEARCH. IT IS NO WONDER THAT YOUNG SCIENTISTS, THOSE UNDER 40, ARE DEEPLY CONCERNED, AS JIM WATSON AND JOHN TOOZE RECOUNTED AT THE MEETING 2 WEEKS AGO SPONSORED BY THE HOWARD HUGHES MEDICAL INSTITUTE.

THIS IS OUR DILEMMA. HOW DO WE ASSESS THE ODDS OF BEING ABLE TO, AT LEAST SUSTAIN, OR, MORE IMPORTANTLY, INCREASE THE INVESTIGATOR-INITIATED BIOMEDICAL RESEARCH ENTERPRISE AGAINST THE NEED TO CONTINUE AN ONGOING, PARTIALLY COMPLETED PROJECT TO CHARACTERIZE THE GENOME.

THIS ENDEAVOR IN HUMAN GENETICS, LIKE ALL SCIENTIFIC ACTIVITIES, IS GLOBAL IN ITS SCOPE AND CLEARLY REQUIRES WORLD-WIDE COORDINATED EFFORTS BETWEEN INDIVIDUAL SCIENTISTS, BETWEEN INTERNATIONAL RESEARCH INSTITUTIONS, AND BETWEEN A NUMBER OF FEDERAL AGENCIES INVOLVED IN BIOMEDICAL RESEARCH. AS THE LARGEST BIOMEDICAL RESEARCH INSTITUTION, NIH HAS AN IMPORTANT ROLE.



222

TO HELP DETERMINE WHAT THAT ROLE SHOULD BE AND WHETHER TO EXPAND OUR EFFORTS AROUND WHAT IS NOW AN ESSENTIAL CENTERPIECE OF ALL GENETIC RESEARCH, GENBANK<sup>®</sup>, I WILL CONVENE THE ADVISORY COMMITTEE TO THE DIRECTOR, NIH, ON OCTOBER 16 AND 17. SOME OF YOU ARE ALREADY HELPING US PLAN THIS MEETING. SOME OF YOU WILL PARTICIPATE. WE WELCOME ALL VIEWS. ALL ASPECTS MUST BE TAKEN INTO ACCOUNT, INCLUDING THE WORST AND THE BEST SCENARIOS THAT WE CAN ENVISION.

THE DEBATE MUST BE CONTINUED AND EXTENSIVE. WE OWE IT TO THE MEMBERS OF THE BIOMEDICAL RESEARCH COMMUNITY, BOTH THOSE WHO ARE WELL ESTABLISHED AND THOSE BEGINNING THEIR CAREERS, AND TO THE PEOPLE OF THE WORLD TO DETERMINE THE APPROPRIATE BALANCE AND TO TRY TO PREDICT AND PLAN FOR THE IMPACT OF THIS TYPE OF EFFORT ON FUTURE INNOVATIVE, CREATIVE RESEARCH ENDEAVORS. ONLY THEN CAN NIH AND ALL OF US DECIDE WHAT OUR ROLE SHOULD BE IN THIS PROJECT, WHICH SEVERAL OF YOU HAVE CALLED "THE GREAT EXPERIMENT."

228

OPENING REMARKS\*

BY

JAMES B. WYNGAARDEN, M.D.\*\*

President Páí Losonczi, Honored Platform Guests, Ladies and Gentlemen: I am honored to be here in beautiful and historic Budapest this evening for the opening ceremonies for the 14th International Cancer Congress. I bring greetings from the National Institutes of Health and best wishes for a successful meeting.

We at the National Institutes of Health are now preparing to observe our 100th anniversary, starting in October of 1986. In this connection, it has been particularly interesting to consider the role that the National Cancer Institute--which is about to celebrate its 50th anniversary--has played in the mosaic of the Federal biomedical research effort.

The NIH itself had its origins in 1887 in a one-room, one-man laboratory in New York City and functioned for its first 40 years essentially as a free-standing infectious disease research lab. The National Cancer Institute originated in 1938 when President Franklin D. Roosevelt signed the National Cancer Institute Act, making the NCI essentially a sister agency of the NIH. Just three months

---

\*Opening Ceremony of the 14th International Cancer Congress, Budapest, Hungary, August 21, 1986.

\*\* Director, National Institutes of Health, Bethesda, MD.

later, the NCI made its first fellowship awards in cancer research. In 1944 the NCI became a part of the NIH, and in 1948 a second categorical institute--the National Heart Institute--was created. Now twelve separate entities make up the organization.

The National Cancer Act of 1971 greatly expanded the NCI, which today receives nearly one-fourth of the total NIH appropriation.

The New National Cancer Program had two important features: first, markedly expanded support for basic research; and second, program support for the application of the results of research. This second portion was a very important feature of the program. The intent was to give the National Cancer Institute the tools to apply the results of basic research as they were discovered. This was the clear intent of the Congress in an era when NIH was faulted for not being aggressive enough in "translating" the fruits of research into the practice of medicine.

The National Cancer Program has evolved rapidly since the passage of the Act in 1971 and its amendments in 1974.

It provided training programs in research and clinical medicine. Using funds provided by the Act, we went from fewer than 100 medical oncologists to more than 3,000 today; from a few hundred radiation oncologists to about 1,900 today.

It allowed the NCI to establish a program to monitor cancer incidence and survival nationwide. This is

necessary for tracking progress and setting national goals.

It established a cancer control program--which today is using information on cancer prevention in a prospective way.

It expanded our clinical trials program to study new or revised cancer treatments.

And, it established a network of cancer centers for generating new ideas and for applying the results of basic research to benefit people.

International activities have long been a priority of the NIH and the NCI, and the National Cancer Act has intensified our commitment to international programs for control, prevention and eradication of cancer. These efforts include: support of cancer research conducted by scientists abroad; bilateral agreements (now 10) with foreign government institutions or organizations; liaison with international organizations with high interest in cancer research; and support of training for foreign scientists in the U.S. as well as interaction of American scientists with their colleagues in laboratories abroad. Such programs received important impetus following the November 1985 Geneva summit when a joint statement was issued by President Reagan and General Secretary Gorbachev calling for an expansion of U.S-U.S.S.R exchanges in health research, particularly renewed cooperation in the area of cancer.



Communication and exchange of ideas is of utmost importance in research. Therefore, the NCI operates an International Cancer Information Center for sharing of information on cancer research, treatment, prevention and control on a worldwide basis.

This international congress, too, can be expected to make major contributions to enhanced international cooperation--not only through the wealth of new scientific information presented as formal agenda items, but also through the less formal discussions and exchanges which are a highlight of this international meeting.

And to you, President Lapis and Secretary General Eckhardt, our profound gratitude for your superb hospitality.

## COLLOQUIUM ON THE FUTURE OF BIOMEDICAL COMMUNICATIONS\*

by

James B. Wyngaarden, M.D.\*\*

An organization's 150th anniversary provides a great excuse for doing a lot of things--for example, celebrating accomplishments, spreading the word about current services, examining "roots" as you did this morning, and . . . looking towards the future. While some might be happy to speculate rhetorically about the great things to come, I am glad to say that the Library has taken a much more rigorous and practical approach to the subject.

In January 1985, the Library's Board of Regents suggested that NLM develop a long-range plan to guide it through the future decades. The planning the Board was talking about was not just a list of general goals and checkpoints for management, it was a comprehensive plan that would involve all of the various constituencies among the Library's users and would enlist their support in achieving that future.

Dr. Lindberg and his staff responded to this suggestion with impressive commitment and imagination. The NLM planning involved librarians, physicians, nurses, and other health professionals, basic biomedical scientists, computer scientists, and a number of other groups whose interests overlap with the Library's mission. Some 85 experts eventually served on the five planning panels established to deal with five specific domains of the Library.

With one exception, this afternoon's speakers chaired these panels. I should point out that their topics for today were not limited to the subjects of their panels: they are free to talk on any topic they wish related to the future of biomedical communications.

Perhaps I should not overemphasize the pragmatic nature of planning for the future. As the Library's yearlong celebration has repeatedly pointed out, there is art as well as science connected with greatness. The important figures of the Library's distant--and recent--past had, and have, impressive qualities of vision and character, of imagination and dedication to service, qualities that underpin all of the practical work necessary for planning for the future.

I would be remiss if I did not also mention NIH's 100th anniversary which we will all begin celebrating next month. Like NLM, we will be focusing on the past as well as future, and dealing with a theme that will be exemplified here today--the theme of partnership involving the worlds of academia, business, and government.

---

\*Presented at the National Library of Medicine Sesquicentennial Celebration, Lister Hill Center Auditorium, on September 16, 1986, at NIH.

\*\*Director, National Institutes of Health, Bethesda, Maryland.

Ralph Waldo Emerson wrote, " . . . the past instructs; the future invites." He might have added that the future invites especially those who have been well instructed by the past. Our speakers are all qualified not only by their accomplishments in a variety of disciplines--in medical as well as information fields--but also by their enthusiasm and realism in addressing the topic at hand.

## NURTURING THE BIOMEDICAL RESEARCH ENTERPRISE\*

by

James B. Wyngaarden, M.D.\*\*

I am honored indeed to have been asked to participate in the Research Week Program of the University of Puerto Rico Medical Sciences Campus. Such an occasion has a special personal significance to me for it brings together the two areas--research and medical education--to which I have devoted myself since finishing medical school. During my 25 years as a medical school faculty member I was involved continuously with research but, since becoming a full-time research administrator as Director of the National Institutes of Health (NIH), I have been engaged outside the academic setting. For that reason I take special pleasure in being a part of this activity involving faculty, students, and research personnel.

The fact is, however, that in research one is never far removed from academia and, similarly, in academia one is never far from research. The scheduling of this week's program at the beginning of a school year is timely and appropriate.

Today I wish to speak generally about the challenges and opportunities that lie ahead for biomedical research in the United States in the closing years of the 1980s.

In my discussion I will speak principally of the National Institutes of Health, but inasmuch as NIH funds about 90 percent of basic biomedical research and over 60 percent of clinical research in the U.S., it seems reasonable to project from it to the outlook for biomedical research in our country in general. Because I am an optimist about the future of the NIH, I view the future of biomedical research with optimism. Despite current fiscal pressures, it is my conviction that the road ahead for the NIH is promising. I base this belief on the commitment of the Federal Government to the support of biomedical research for the improvement of human health--a commitment that is steady and strong in both the executive and legislative branches.

Before discussing in some detail the programs of the NIH, I will sketch in broad outline some pertinent facts about the research enterprise in the U.S.

- o The total national expenditures for health research and development during 1985 were estimated at \$13.5 billion. The Federal Government was the source of just over one-half of the total or about \$6.8 billion. The NIH expended \$4.8 billion, or over 35 percent of funding for health research and development in the Nation. All of the Nation's industries together spent about 37 percent or slightly more than the NIH share.

---

\*Presented at the University of Puerto Rico Medical Sciences Campus, San Juan, September 22, 1986.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



- o This comparative increase in industrial participation in health R&D is recent. Ten years ago industry's expenditures amounted to a substantially smaller share--27 percent.

Along with increased expenditures new and mutually beneficial relationships have been developed between industrial organizations and a number of academic institutions. Among these institutions is the University of Puerto Rico. Some of the cooperative activities sponsored by pharmaceutical and chemical companies have enabled the University to carry out needed educational and research activities date back to 1981. Just a year ago, in September 1985, these relationships were strengthened through the creation of a University-Industry Research Program in Pharmaceutical/Chemical Sciences. The partners in this relationship are advancing basic and applied research, education, and training in ways that none of the participants could accomplish alone.

As I have come to know more about individual examples of such arrangements, I have been interested to note the many ingenious contractual arrangements that have been devised to serve optimally the purposes of the partners while protecting their interests with respect to freedom of inquiry, open scientific communications, and proprietary rights.

The NIH has a deep and abiding interest in such new partnerships but has not interposed itself in them.

#### NIH Since 1945

- o The NIH shortly will begin observance of its centennial, celebrating "a century of science for health." There are many fascinating stories of human courage and of brilliant scientific achievement in the institution's history. For today's discussion, however, I will confine historical references to budgetary trends and policy developments of the past 40 years.
- o The period since the end of World War II is the era of the modern NIH--the agency as we know it today. Prior to the War, almost all of its research had been in-house. After 1945 the partnerships that had been established with universities, medical schools, hospitals, and other research institutions in the War effort were continued and, in fact, strengthened. Currently about 88 percent of NIH funds are committed to extramural research and training.
- o Every year since 1945, with only a few exceptions, the annual NIH budget has increased. For a part of that time, until 1968, the increases were spectacular. From 1945 to 1968 the budget grew at an astounding average rate of 24 percent per year. (Slides 1A and 1B)

#### Adjusting to Deceleration in Budget Growth

- o By 1970, due largely to the budget stresses of the Vietnam War, the NIH appropriation took at least one step backward. Some saw the reduction as the "beginning of the end of Federal support for biomedical research." It was, in fact, the "end of the beginning." Even so, the NIH budget has not, since then, been reduced from one year to the next.
- o The growth rate since 1968 has averaged about two percent per year in purchasing power. (Slide 2)

- o By 1970 a well-planned initiative led to the "war on cancer" with the President and the Congress vying for the leadership in providing funds and organizational innovations for the conquest of cancer. Between 1971 and 1973 the budget of the National Cancer Institute more than doubled in current dollars. It had tripled by 1975.
- o The National Heart, Lung, and Blood Institute also experienced a period of rapid growth, increasing by 54 percent between 1971 and 1973, and doubling by 1977.
- o The budgets of both NCI and NHLBI grew faster than the total NIH budget during the early and mid '70s. By the end of the decade, however, the growth differential generally disappeared.
- o Beginning in the early 1970s and continuing to the present, another set of program adjustments has taken place involving shifts among the mechanisms used for funding research. Priority was given to research project grants with a concomitant reduction in budget for research contracts and training. (Slide 3)

#### Priority for Project Grants and Heightened Competition

- o The total number of project grants supported in 1972 was 10,290; by 1985, the total had grown to 18,219. In this period the average award per project remained virtually unchanged in constant dollars. The average in current dollars, however, increased from \$59,000 in 1972 to \$147,000 in 1985. (Slide 4) But indirect costs took an increasing share of the research award, rising from 21 percent in 1972 to 31.3 percent in 1985. (Slide 5) Consequently, the average real support available per project for direct costs was reduced, or at best was unchanged.
- o The progress of science has resulted in an increased number of grant proposals. A total of 18,675 competing research grant applications were reviewed in 1985. In 1976 the total was 10,050; and in 1971 less than 8,000. (Slide 6)
- o We have become increasingly concerned about maintaining a relatively stable and predictable level of new and competing renewal grants. The number of competing awards fluctuated widely over the past decade, from a low of 3,464 in FY 1976 to a high of 6,247 in FY 1985.
- o We made it a major goal of our original "stabilization initiative" to fund at least 5,000 new and competing renewal grants each year atop the moral commitments of some 11,000 continuation grants. In all but three of the past 10 years we have awarded at least 5,000 new and competing renewal awards. Budget limitations, however, have precluded a comparable degree of stability for other research and training programs of the NIH.
- o However, in spite of the progressive annual shift of funds into research project grants, the number of applications has grown faster than resources.  
  
In 1976 we could fund about 48 percent of grants eligible for award but, in 1984, 1985, and 1986, we were able to fund only about 37 percent. As would be predicted, the paylines are progressively lower. (Slides 7 and 8)

### Side Effects of Increased Competition--Stresses on the Peer Review and Awards System

- o Another result of fiscal constraints plus increased competition is the increasing frequency with which grant proposals are being resubmitted after unsuccessful competitive review. In 1965, six percent of applications reviewed were resubmissions; in 1975, 15 percent were resubmissions; and by 1985 the proportion of resubmissions was about 25 percent of all applications. As might be expected, resubmitted applications enjoy a higher success rate than de novo proposals, reflecting heightened influence of the study section on the form and substance of grant applications.
- o In response to the tougher competition and the widespread perception that study sections often look for minor flaws or omissions in proposals under review and that small factors shift priority scores, applicants tend to over document. As a result, the workload for both the applicant and the study section is greatly increased.
- o Although fiscal constraints are responsible for much of the difficulty experienced by the research community, certain attributes of the current extramural award system may be more burdensome than necessary for the investigator, the grantee institution, and the NIH peer review system. In order to increase productivity with the resources available to us, we have instituted several changes in the review and award process.
- o In our judgment one of the factors that is contributing needlessly to the workload of both the grant applicant and the NIH peer review system is the excessive complexity and sheer bulk of the research grant application. In addition to proposing page limitations for grant applications, we have taken other steps to reduce the reviewing time for study section members as well as preparation time for the applicant.

### FIRST and MERIT Awards

- o We have observed that, when the award rate falls, the percentage of successful first-time applicants also falls. It is essential to the vitality of the scientific enterprise and to the morale of the scientific community that young scientists be encouraged. We recently announced a new program called FIRST awards (First Independent Research Since Training)--a modification of the R-23s which lengthens the awards from three to five years and the total to \$350,000 of direct costs for the five years. This should obviate the need for too early reapplication for investigators who encounter difficulties in the first 18 months of grants. It will, we believe, encourage more creative and less defensive research.
- o Further, we have expanded the number and types of longer term support for outstanding mid-career scientists through a new program called MERIT awards (Method for Extending Research in Time). This program will involve facilitated extensions of 5-year awards for an additional three to five years on the basis of a detailed progress report, rather than through reapplication. (The extension will be tallied as a competing renewal.)



### Research Training and Career Development

- o There are two general categories of NIH training programs--those funded through National Research Service Awards (NRSA) and those encompassed in the more advanced career development series.
- o Individual fellowships are awarded through national competition under NRSA. Institutional awards under the NRSA program permit institutional selection of trainees at both the predoctoral and postdoctoral level. The medical science training program (the so-called "MD-PhD" program), supported through institutions within the NRSA program, is considered to be one of the most successful in an area critically important to the future.
- o The 1985 appropriation permitted a substantial increase of stipends in postdoctoral categories making the income for clinical postdoctoral fellows and trainees more compatible with that of house staff. Equity was maintained for the Ph.D. who, after two years of postdoctoral training, is contributing in an important way to research activity. Postdoctoral stipends were increased, so that with funds for tuition and other expenses, our total outlay per student per year became essentially the same as that offered by the National Science Foundation.
- o Opportunities for advanced research preparation are offered through the NIH Research Career Development Program. The oldest of these is the Research Career Development Award (RCDA), solely for salary and fringe benefits. More than 80 percent of those who have received RCDAs now have research project grants. Other K Series awards include: the Academic Investigator Award, the Clinical Investigator Award, the Mid Career Development Award, and the Physician/Scientist award. These awards provide a salary of up to \$40,000 plus applicable fringe benefits. The actual salary is intended to be comparable to that of others at the same institution at the same level of training and experience.
- o The 1985 appropriation provided over \$217 million for 10,623 NRSA fellows and trainees. The 1986 appropriation (after Gramm-Rudman) is for \$209 million and will support 9,947 NRSA fellows and trainees.

Our budget for career development programs in 1985 was over \$76 million, supporting 1,318 awards. The 1986 budget for career awards is about \$100,000 lower than last year's and provides for 44 fewer awards.

Another facet of the NIH training, career, and research programs is the Minority Biomedical Research Support Program (MBRS). This program is a direct response to the inadequate representation of minorities in biomedical research. Efforts to increase the number of minority scientists in biomedical research are carried out by bolstering research activities at eligible institutions fostering faculty and student participation in biomedical research, thereby helping to create a growing number of minority scientists who are making important contributions in the health sciences.



In 1986 the University of Puerto Rico received six MBRS awards for a total of \$2.8 million. Two of the grants were made to the Rio Piedras Campus, and one each at the Medical Sciences Campus, Mayaguez Campus, Humacao University College and Cayey University College. The research involves a broad spectrum of biomedical investigations relevant to the mission of the NIH; 20 of the total 57 research projects are supported through co-funding by seven different NIH institutes.

The largest of these programs is administered through the Rio Piedras Campus and supports 32 projects there involving 46 graduate and 53 undergraduate students.

At the Medical Sciences Campus there are 12 investigators supported through the Medical Sciences Campus grant. Another 15 medical sciences faculty are supported through the MBRS grant made to the Rio Piedras Campus, primarily for student involvement in research at the Medical Sciences Campus. On the Medical Sciences Campus, 24 students are participating in these grant supported projects. Another 99 are involved in the Rio Piedras grant, and 33 students are involved in the research at the regional colleges and the Mayaguez Campus.

The MBRS program has opened opportunities for numerous investigators in Puerto Rico to develop their biomedical research capability and involve its students in research.

Two applications for support through the RCMI, or the Research Centers in Minority Institutions Program, were recently submitted by the University of Puerto Rico, one from the Medical Sciences Campus and the other from the Rio Piedras Campus. Both applications have been reviewed and approved by the National Advisory Research Resources Council of the Division of Research Resources.

The Medical Sciences' application includes support to strengthen the infrastructure in order to make the institution more competitive for NIH and other research grant support. A newly established division of research support services will be provided partial support for a number of shared resources including a computer/biostatistics unit, a flow cytometry and tissue culture laboratory and a protein and physical biochemistry laboratory. This latter laboratory would be the first of its kind in the Caribbean Basin. Support for these resources should enhance the Medical Science faculty's capability to conduct biomedical research.

RCMI support for the Rio Piedras Campus will be used to develop further research in the areas of cell and molecular biology, synthetic and natural products chemistry and photobiology and photochemistry. From the faculty research competence and strong commitment which the University of Puerto Rico has made to support biomedical research, it is clear that the institution's capacity to conduct biomedical research will be significantly enhanced through RCMI support. Awards to both campuses thus are likely before the end of this month.

I will turn now to some matters of general interest and concern to the Nation's biomedical research community.

## Instrumentation, Facilities and Laboratory Animals

- o Over the past decade increasing concerns have been expressed regarding obsolescence of research instrumentation and facilities in the Nation's research institutions. A study on instrumentation jointly funded by the National Science Foundation and the NIH was completed last year. The report showed a national need for newer equipment in many laboratories, particularly public institutions. The outstanding need seems to center on relatively low cost instruments in the \$10,000 to \$75,000 range, perhaps reflecting some degree of success in warding off critical needs for large instruments through ongoing NIH programs for sharing such instruments. It was under one such program, for example, that the 1985 grant was made to the University for a fluorescent Activated Cell Sorter for cell biology research participated in by several investigators who share the use of the instrument. Another example is the "Prophet" computer site supported at the Medical Sciences Campus that links most of the researchers at the University Campuses to the Prophet Computer System supported through the NIH's Division of Research Resources. This provides a powerful computer capability as well as communications with other laboratories on the mainland.
- o For a number of years the condition of academic research facilities has steadily deteriorated. Federal support in this area has been limited and diminishing. The extent of the need for Federal support of health-related research facilities is difficult to ascertain since no comprehensive assessment of this need has been made since 1968.
- o During the past century virtually every major development in biomedical research has depended at some point upon the use of animals. A small but determined segment of society is opposed to the use of animals in research, and they are bringing increasing pressure on scientists, physicians and many institutions, staging sit-ins, demonstrations, as well as vandalism, break-ins and bomb threats against investigators and others associated with studies requiring animals.

I am pleased to say that NIH and other defendants earlier this month won a court case that had been brought in the United States Court of Appeals (Fourth Circuit) by three animal rights groups and some individuals. The plaintiffs demanded custody of the well-known Silver Spring monkeys. A judge had put these 15 monkeys in NIH's interim custody after the principal investigator had been charged with animal cruelty--a charge that was later dismissed. The animal rights people asserted that they had standing to sue because they were taxpayers and also helped support the monkeys after the owner gave them up temporarily. They also said they were promoting the humane treatment of animals and that they had a personal relationship with the monkeys.

The language of the Court's decision is worth quoting to you:

"To imply a cause of action in these plaintiffs might entail serious consequences. It might open the use of animals in biomedical research to the hazards and vicissitudes of courtroom litigation. It may draw judges into the supervision and regulation of laboratory research. It might unleash a spate of private lawsuits that would impede advances made by medical science in the alleviation of human suffering. To risk consequences of this magnitude in the absence of clear direction from the Congress would be ill-advised. In fact, we are persuaded that Congress intended that the independence of medical research be respected and that administrative enforcement govern the Animal Welfare Act."

We are greatly heartened by this common-sense action by the Judges of the Court of Appeals.

Permit me to turn now to the state of the NIH budget for FY 1987.

#### Appropriations for FY 1987

- o The House and the Senate have passed an appropriation bill for NIH for FY 1987.

By a vote of 328 to 86 the House passed an appropriations bill that would increase the NIH budget by 17 percent to a total of about \$6.15 billion.

The Senate passed the NIH Appropriation by a vote of 83-2. The total approved, \$6.12 billion, was slightly less than the House amount. Inasmuch as the appropriation as passed by the Senate differs from the House version, a conference committee will be required.

- o Not only is there uncertainty as to what the two Houses will agree upon as the appropriation for NIH for 1987, there is always the possibility that the President may not concur and his veto be sustained. Furthermore, it is not known at this time what will be the effect of the anti-deficit measures, particularly Gramm-Rudman.
- o In addition to differences in the total amounts appropriated, the Senate and House bills differ on several issues of interest to the NIH and to grantee institutions. The Senate Committee report accompanying the bill made a point of emphasizing a balance in the types of mechanisms used to support research programs, in essence placing emphasis on programs other than research project grants; for example, centers and research training. The House bill had mandated no fewer than 6,200 new and competing renewal grants. Both Houses restored the Biomedical Research Support Grant, which had been recommended for elimination in the President's budget proposal. The question of a limitation on indirect costs was not addressed in the Senate bill, and the House indicated that sufficient funds were included to pay "full direct and indirect costs" of grants.

You may be sure that we will be following closely the progress of the NIH budget.



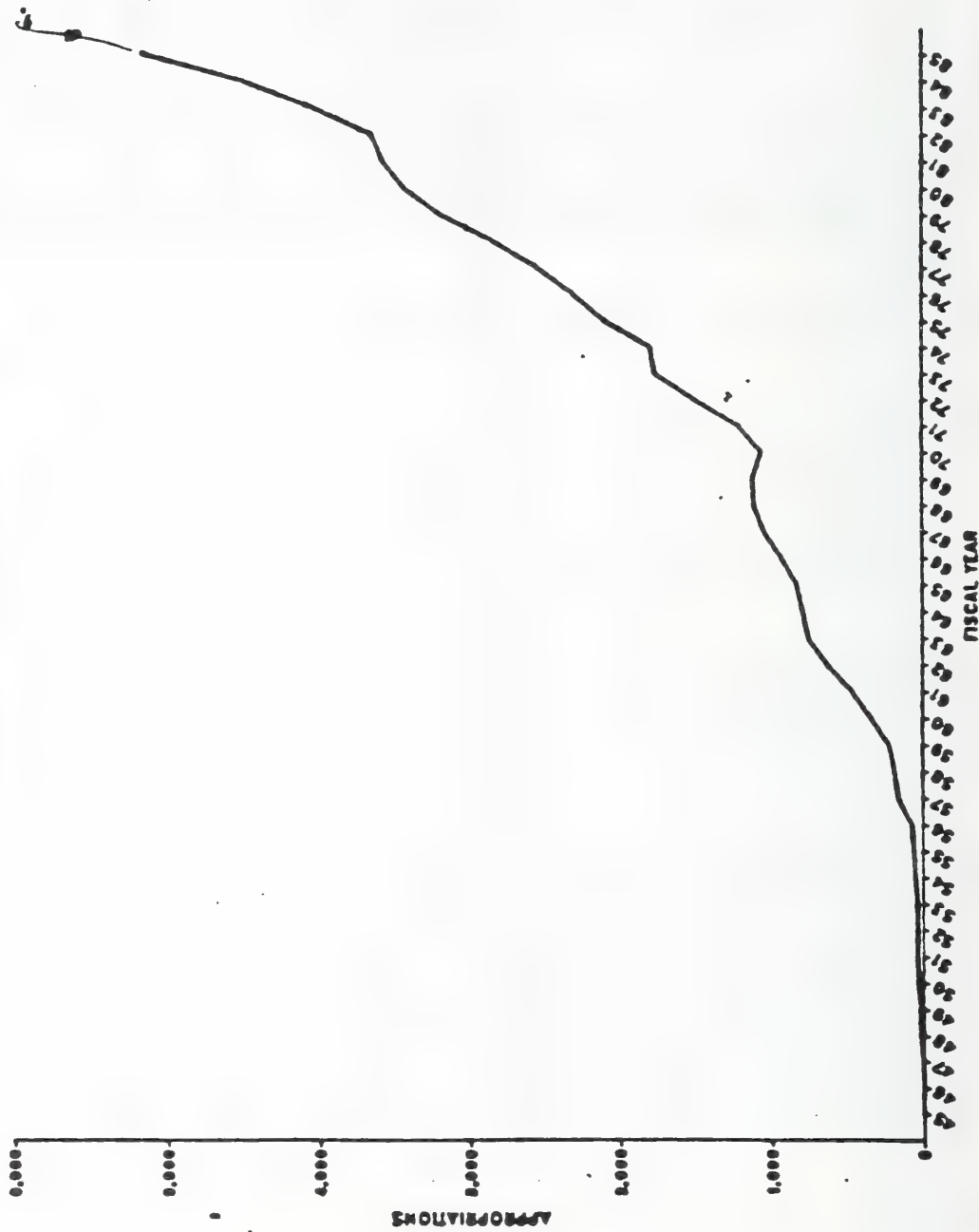
- o At the beginning of this discussion, I told of my optimism about the future of NIH, and spoke of the commitment to biomedical research of both the legislative and executive branches of the Federal Government. In addition to these champions within the Government, we have many strong advocates outside the Government who act on their conviction of the long-term value of research.

Even the Heritage Foundation, not noted for encouraging Federal expenditures, sounded the same fundamental note that has motivated the establishment and growth of NIH. In a proposal by the staff of the Heritage Foundation for the FY 1987 Federal budget, titled, "Slashing the Deficit," the programs of many agencies were examined in detail. Along with a cautionary note as to how NIH might allocate funds more judiciously, the Foundation staff commented, "Basic biomedical research is one of the few activities funded through Washington which is appropriately a Federal responsibility." The writer continued, "Historically, the benefits of such research have outstripped the taxpayers' cost." I could not have said it better.

I will be happy to respond to any questions you may wish to ask.



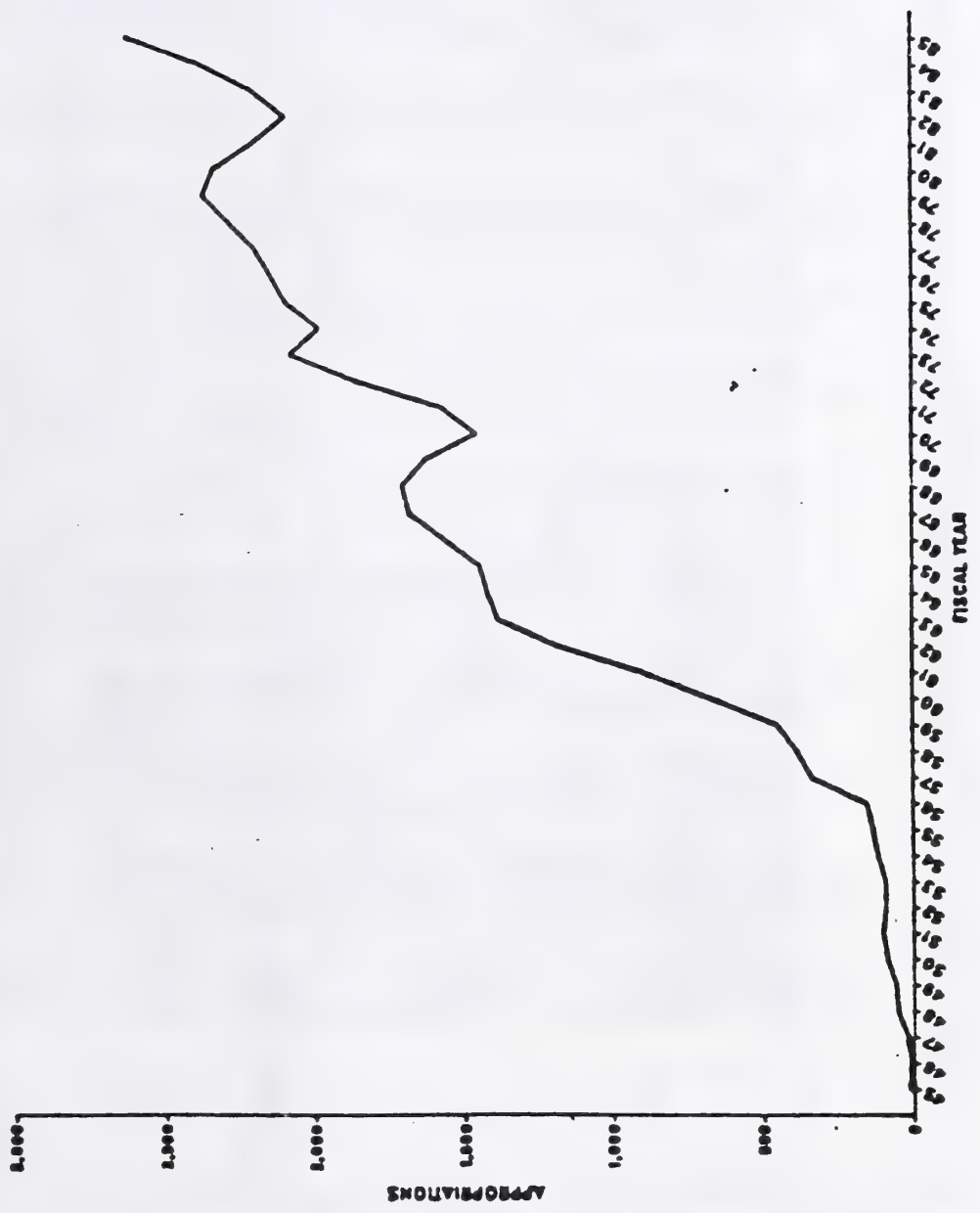
# Total NIH Appropriations in Current Dollars, FY 1945-85 Excluding Programs Transferred Out (Dollars in Millions)



NOTES: TO excluded. 1985 data preliminary.

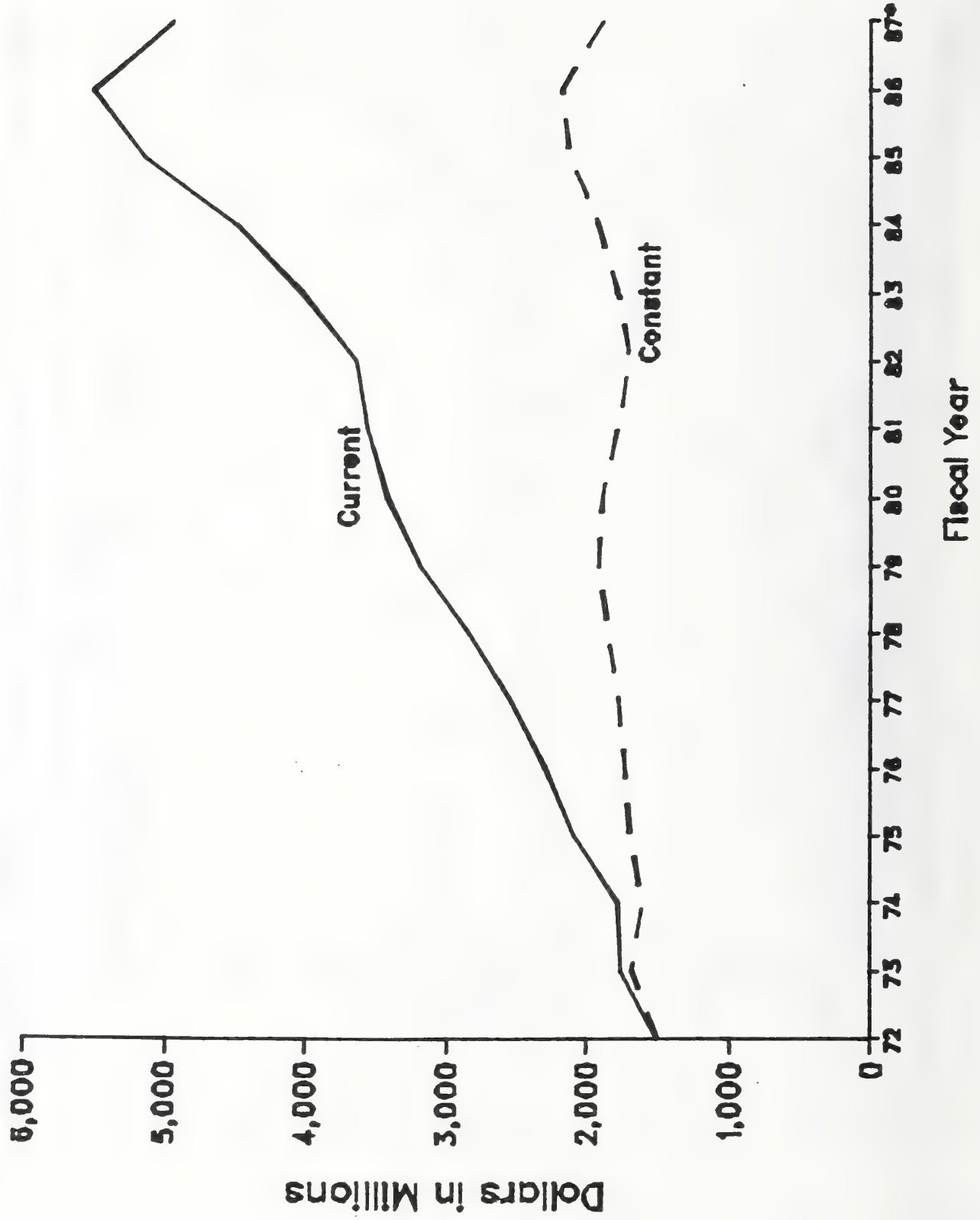
PAB/DPA/OPPE/OD, April 1985

# Total NIH Appropriations in Constant (1975) Dollars, FY 1945-85 Excluding Programs Transferred Out (Dollars in Millions)



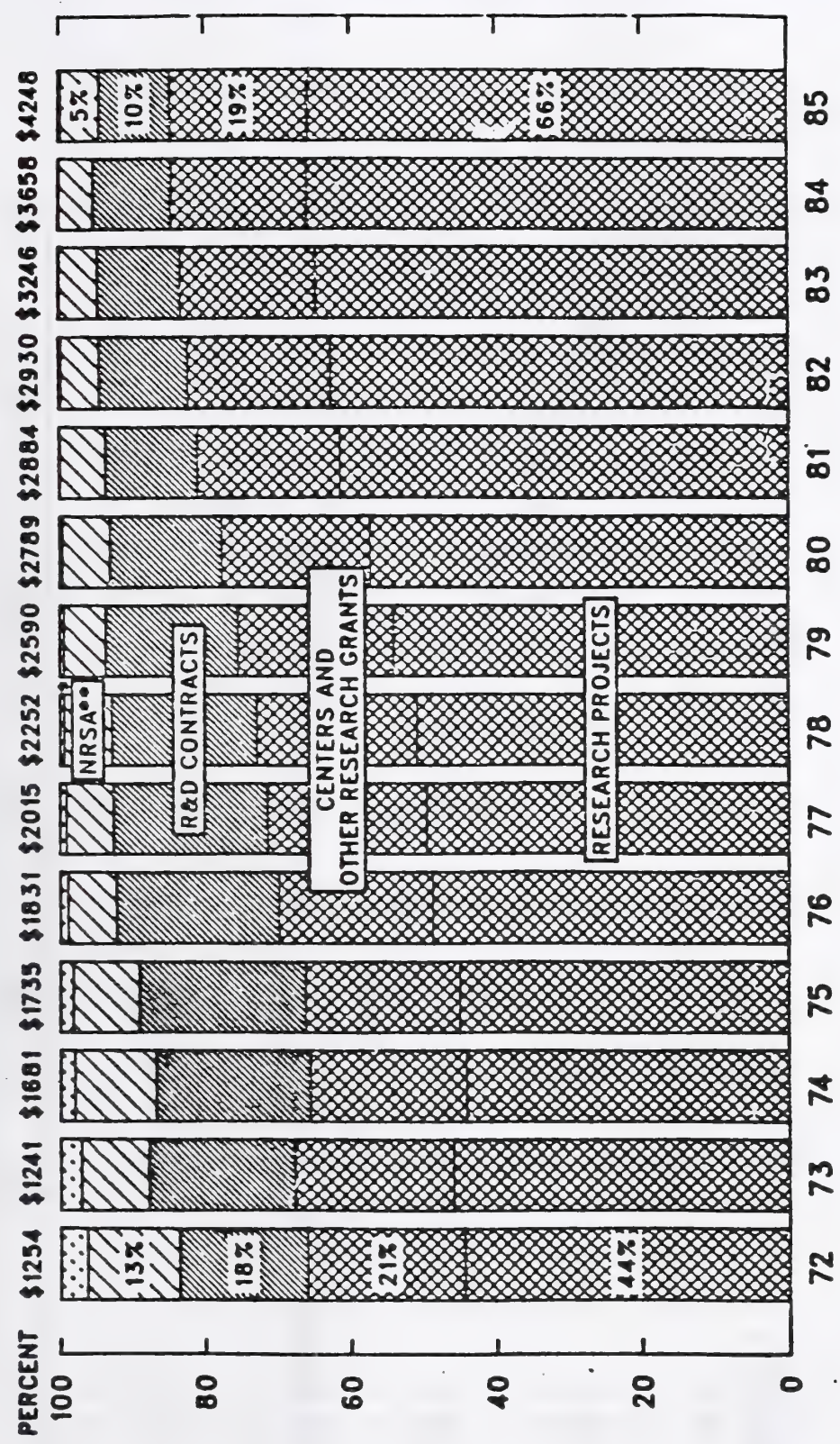
NOTES: Constant dollar conversion uses BRDPL TO excluded. 1985 data preliminary. PAB/DPA/OPPE/OD, April 1985

# Total NIH Appropriations, 1972-87, in Current and Constant Dollars 2.



=estimated

# ALLOCATION OF NIH EXTRAMURAL AWARDS BY ACTIVITY, FISCAL YEARS 1972-1985 PERCENT OF AMOUNT AWARDED (CURRENT DOLLARS IN MILLIONS)



NOTE: EXCLUDES TO. \*INCLUDES CONSTRUCTION AND MEDICAL LIBRARY GRANTS. \*\*INCLUDES PRE-NRSA TRAINING.  
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

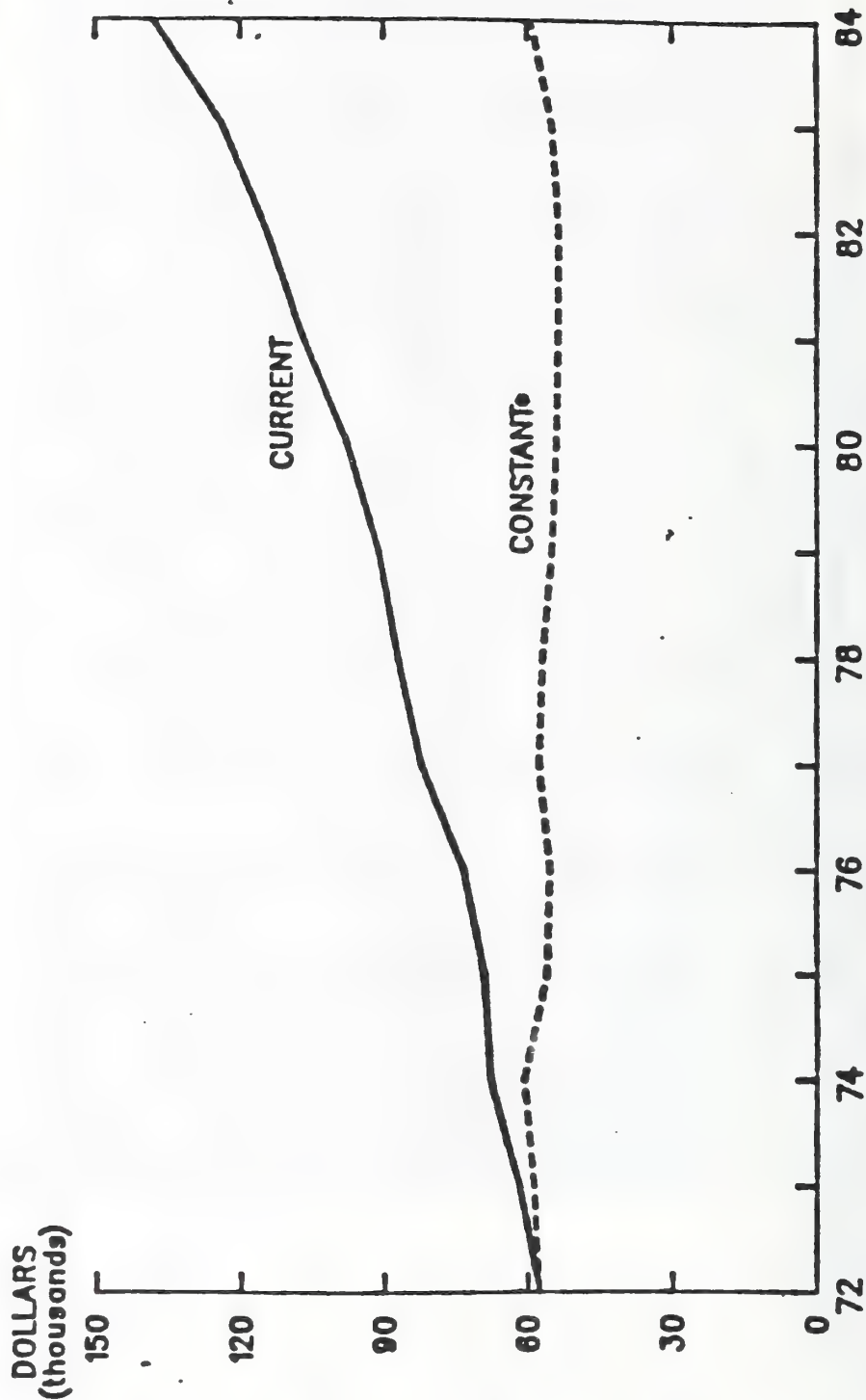
TB-REV.  
6/4/86



4

10/10/78

# AVERAGE DOLLARS FOR NIH RESEARCH PROJECT GRANTS FISCAL YEARS 1972-1984

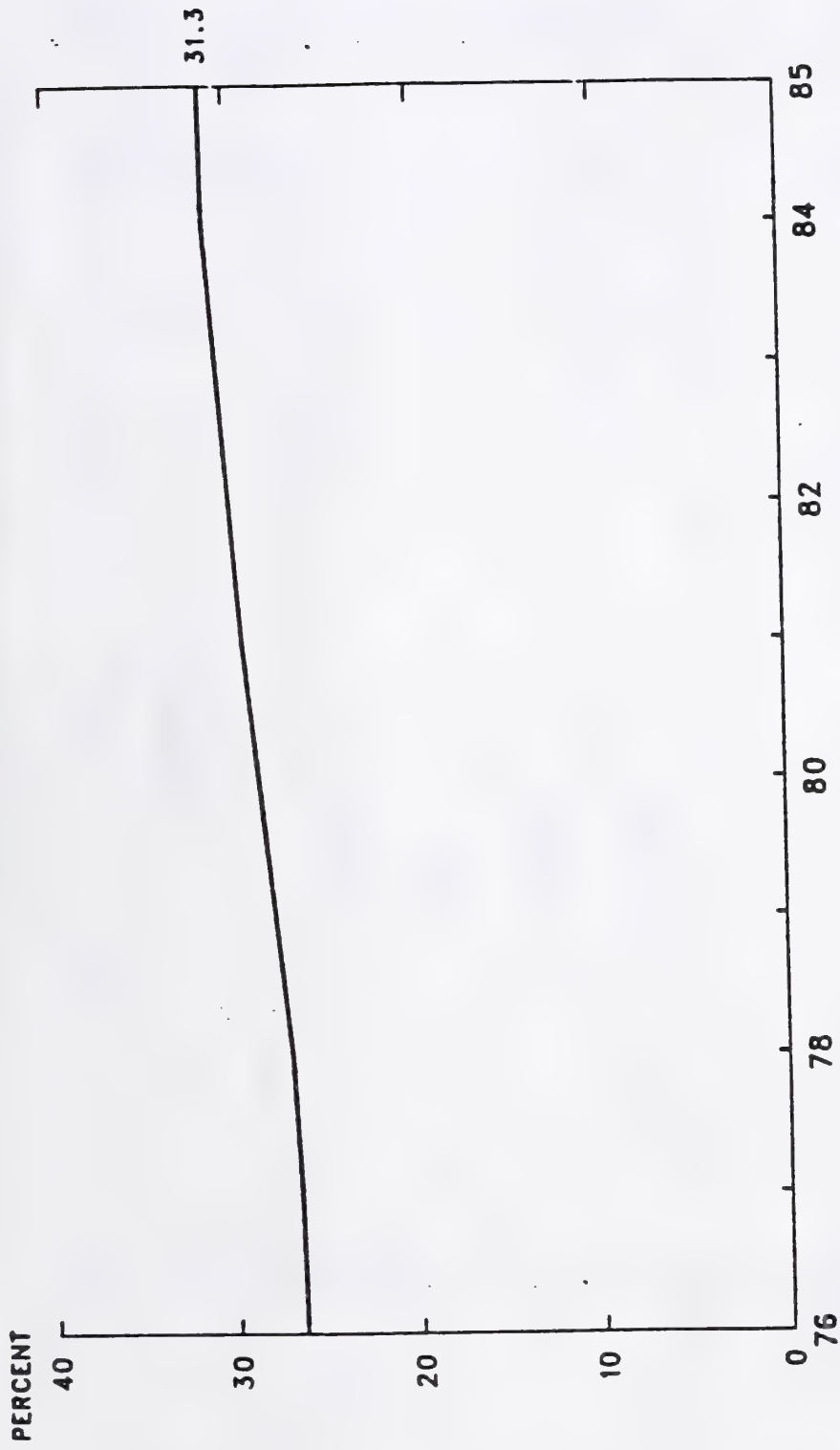


BASED ON BIOLOGICAL AND PRICE INDEX FY1972-100.  
SOURCE: NIH, DHEW, STATISTICS AND ANALYSIS BRANCH

10/10/78

5

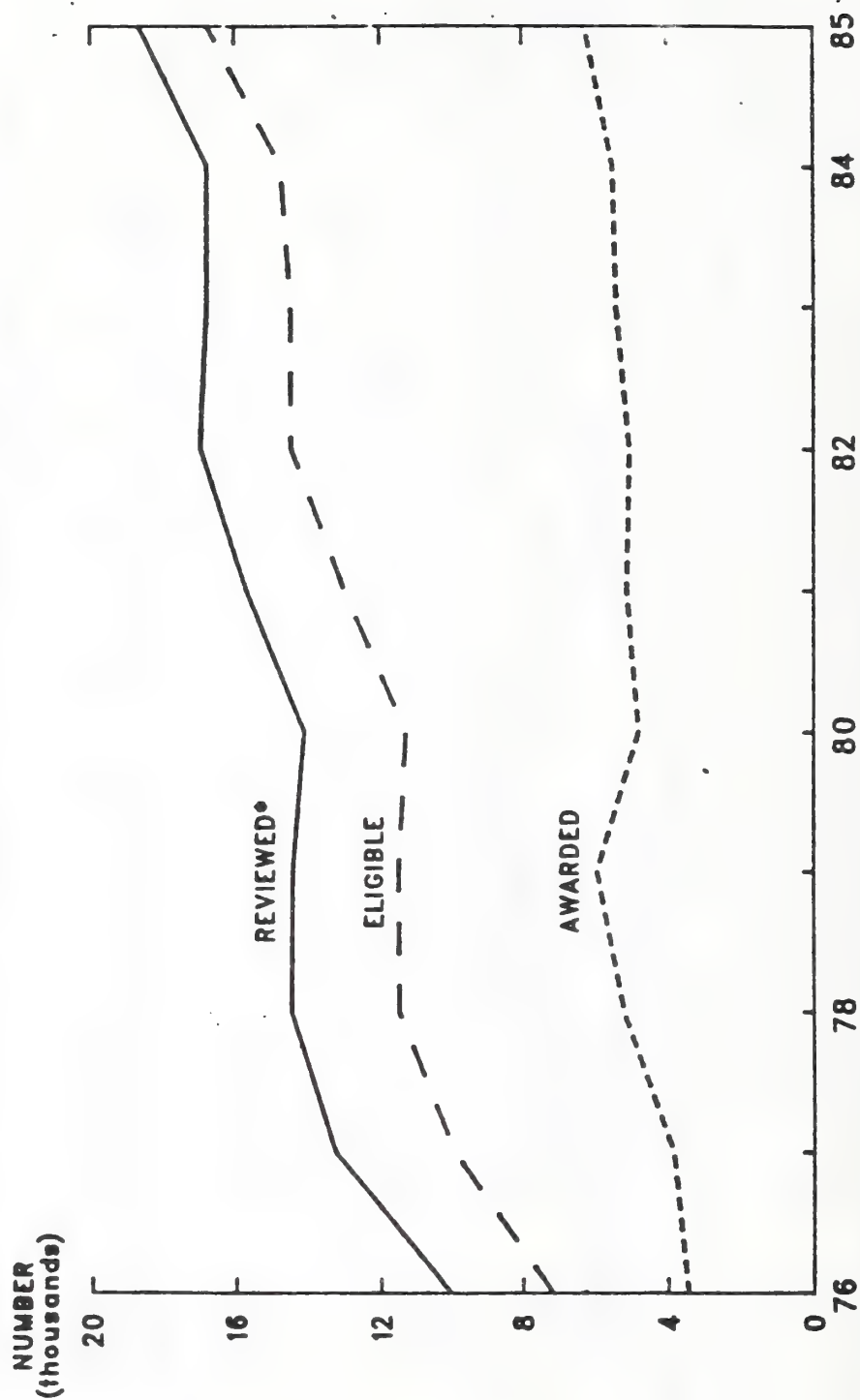
# INDIRECT COST PROPORTION OF TOTAL COST FOR NIH RESEARCH GRANTS FISCAL YEARS 1976-1985



NOTE: EXCLUDES CONFERENCE AND NCI EDUCATION GRANTS, BRD, BRS, RCP AWARDS, AND MINORITY STUDENT APPRENTICE PROGRAMS. EXCLUDES THE TQ. SEE TECHNICAL NOTE ON PAGE III FOR ACTIVITY COVERAGE.  
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

6

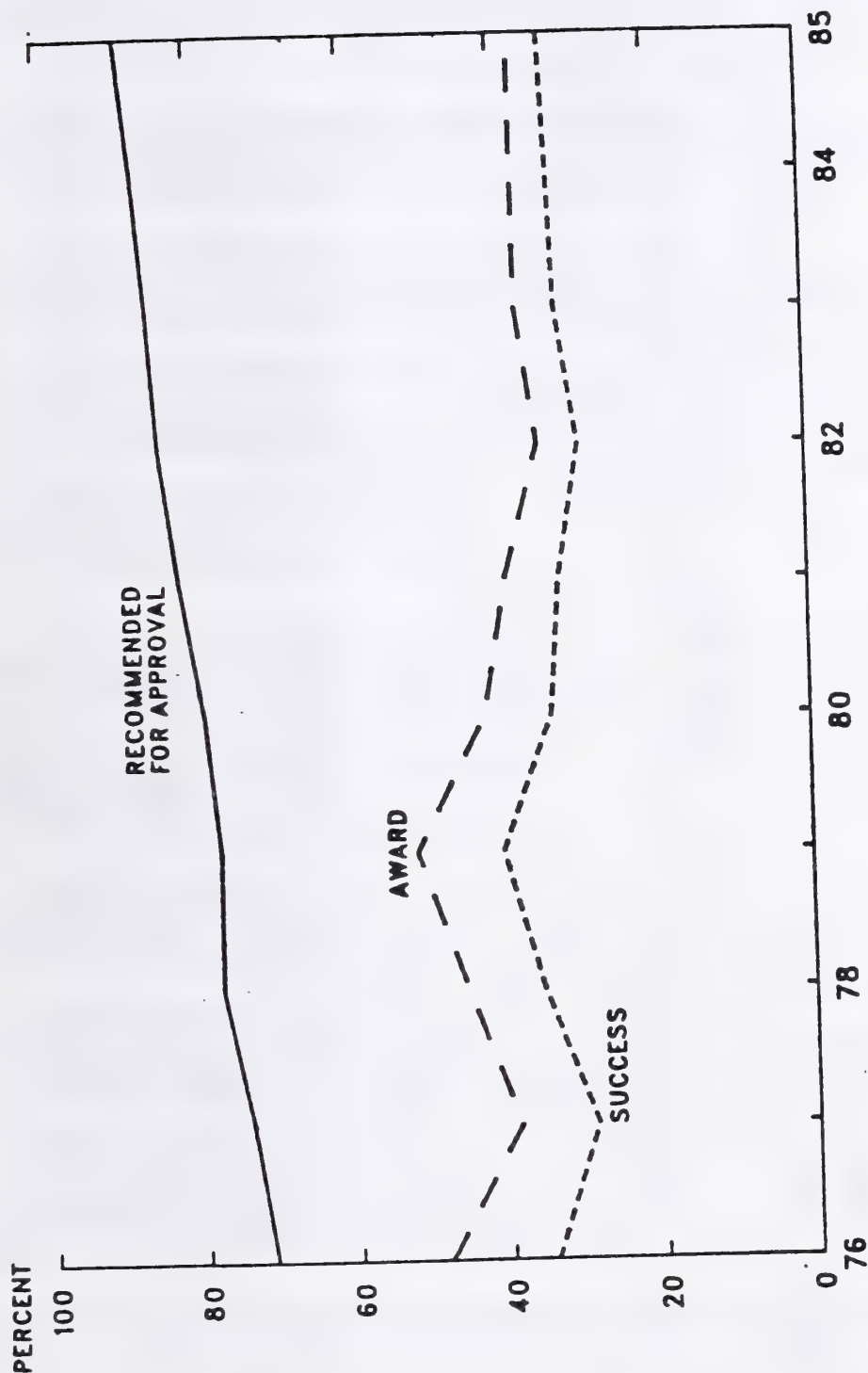
# NUMBER OF NIH COMPETING RESEARCH PROJECT APPLICATIONS REVIEWED, ELIGIBLE AND AWARDED, FISCAL YEARS 1976-1985



NOTE: EXCLUDES TQ. SEE TECHNICAL NOTE ON PAGE III FOR ACTIVITY COVERAGE AND PROCEDURES.  
\*REPORTING YEAR.  
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

7

COUNCIL RECOMMENDED FOR APPROVAL, AWARD, AND SUCCESS RATES  
FOR NUMBER OF NIH RESEARCH PROJECT APPLICATIONS  
FISCAL YEARS 1976-1985

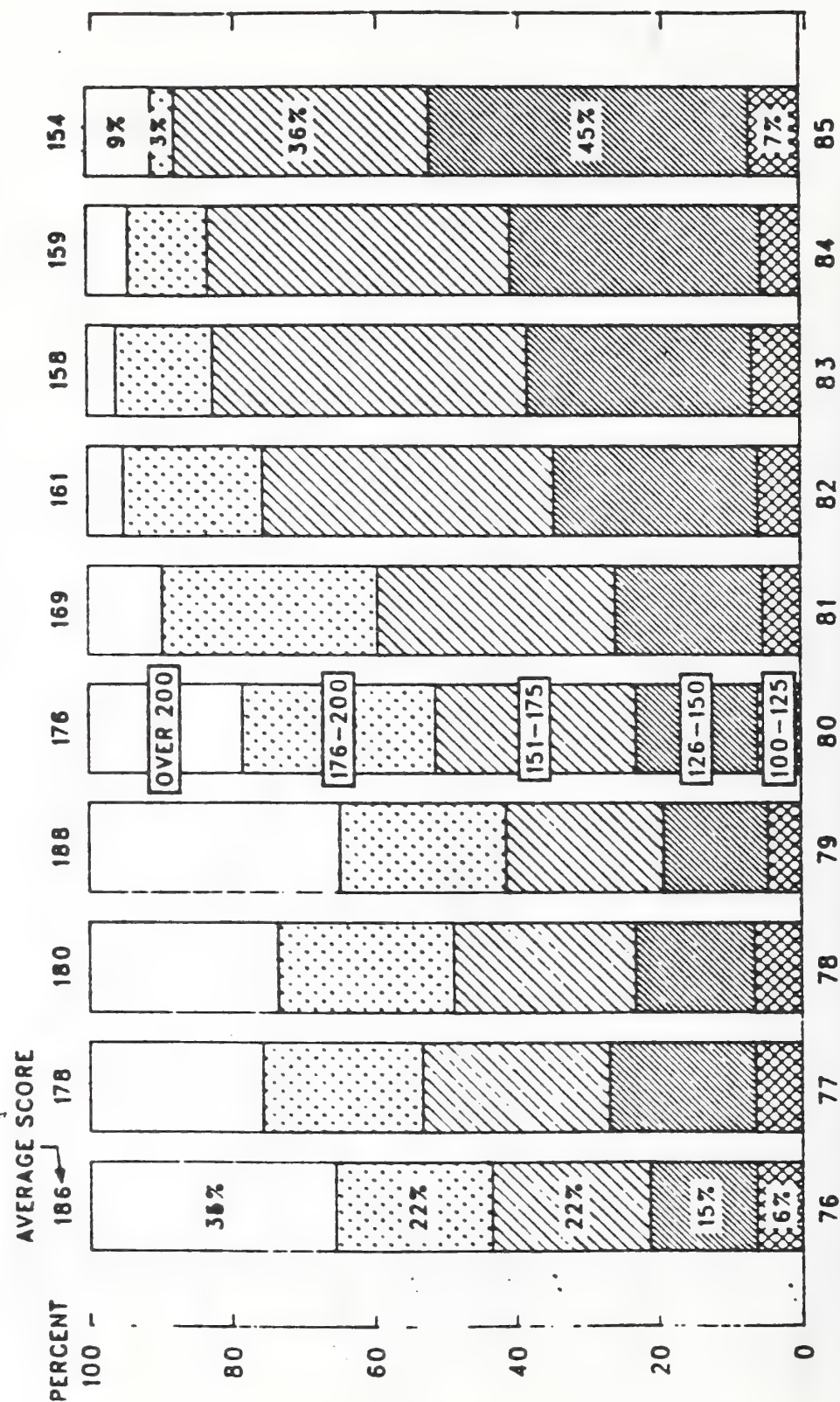


NOTE: EXCLUDES TQ. SEE TECHNICAL NOTE ON PAGE III FOR ACTIVITY COVERAGE.  
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH



8

# DISTRIBUTION OF NUMBER OF NIH COMPETING RESEARCH PROJECTS AWARDED BY PRIORITY SCORE GROUP, FISCAL YEARS 1976-1985



NOTE: BASED ON ACTUAL SCORES. EXCLUDES TQ.  
SEE TECHNICAL NOTE ON PAGE III FOR ACTIVITY COVERAGE.  
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

OPENING REMARKS\*  
BY  
JAMES B. WYNGAARDEN\*\*

GOOD MORNING AND WELCOME TO NIH RESEARCH DAY. AS A "GRADUATE" OF THE NIH INTRAMURAL PROGRAM, I AM ESPECIALLY HAPPY TO BE INVOLVED IN THE KICK-OFF OF THIS UNIQUE EVENT. I SEE THIS AS THE UNOFFICIAL, INHOUSE INAUGURAL EVENT OF NIH'S CENTENNIAL YEAR OBSERVATION.

THE FORMAL OPENING OF OUR HUNDREDTH ANNIVERSARY CELEBRATION, OF COURSE, IS SCHEDULED FOR OCTOBER 16, AS A CEREMONIAL EVENT PRIMARILY FOR THE CONGRESS, DEPARTMENTAL OFFICIALS, AND LUMINARIES ASSOCIATED WITH NIH'S HISTORY.

BUT IT IS VERY FITTING THAT AN INTRAMURAL EVENT IS FEATURED EARLY, SINCE--AS YOU KNOW--NIH'S ANTECEDENT OF 100 YEARS AGO WAS THE ONE-ROOM LABORATORY OF HYGIENE IN THE ATTIC OF THE MARINE HOSPITAL ON STATEN ISLAND IN NEW YORK HARBOR. THIS LABORATORY

---

\*NIH RESEARCH DAY, BETHESDA, MARYLAND  
SEPTEMBER 25, 1986.

\*\*DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND

WAS THE DIRECT FOREFUNNER OF NIH--AND WAS STRICTLY AN INTRAMURAL OPERATION. THE EXTRAMURAL PROGRAMS OF NIH DID NOT REALLY BEGIN UNTIL THE 1930's.

BACK IN 1887, THE DIRECTOR OF THE LABORATORY, DR. JOSEPH KINYOUN, WE CAN GUESS, SPENT A LARGE PART OF HIS TIME ON DIRECT SCIENTIFIC INVESTIGATION OF INFECTIOUS DISEASES. HE HAD ONLY A SMALL STAFF TO MANAGE AND CERTAINLY DID NOT HAVE TO OCCUPY HIMSELF OVERLY IN ADMINISTRATIVE CHORES SUCH AS DEALING WITH PUBLIC INTEREST GROUPS OR DEVELOPING AND JUSTIFYING A LARGE AGENCY BUDGET. WE HAVE DOCUMENTATION SHOWING THAT HIS BUDGET REQUEST TO GET THE LABORATORY STARTED WAS ONLY ABOUT \$300!

BUT EVEN IN THOSE EARLY DAYS, WHEN PUBLIC AND SCIENTIFIC CONCERN CENTERED ON THE INFECTIOUS DISEASES, AND THE IMPORTANT SCIENTIFIC DISCIPLINE WAS BACTERIOLOGY, DR. KINYOUN WELL UNDERSTOOD THE IMPORTANCE OF THE EXCHANGE OF IDEAS AMONG SCIENTISTS. BECAUSE THE CENTERS OF SCIENTIFIC EXCELLENCE AT THE TIME WERE IN EUROPE, DR. KINYOUN TRAVELED THERE TO STUDY AND VISIT IN THE LABORATORIES OF PASTEUR AND KOCH. I AM NOT SURE WHETHER HIS \$300 BUDGET REQUEST INCLUDED HIS TRAVEL ALLOTMENT!

TODAY IN THE MODERN NIH INTRAMURAL RESEARCH PROGRAM, INTERNATIONAL INTERCHANGE IS STILL VERY IMPORTANT. BUT PROBABLY EVEN MORE PRODUCTIVE IS THE FERMENTATION OF IDEAS STEMMING FROM THE CRITICAL MASS OF MORE THAN 2500 INTRAMURAL SCIENTISTS WE HAVE

ORGANIZED HERE AND AT OUR OFF-CAMPUS SITES. IF DR. KINYOUN WERE WORKING ON INFECTIOUS DISEASES HERE TODAY, HE MIGHT NOT EVEN HAVE TO LEAVE BUILDING 7 TO DISCUSS HIS LATEST HYPOTHESIS OR EXPLORE AN ALTERNATIVE METHODOLOGY!

EVEN THE CASUAL VISITOR TO NIH--IN THE ELEVATORS, THE CAFETERIAS, AND ON THE PATHWAYS BETWEEN BUILDINGS--CAN GET A FLAVOR OF THE EARNEST INTERCHANGE GOING ON AMONG SCIENTISTS HERE...WHERE THE SCIENTIFIC DISCUSSIONS DO NOT STOP AT LABORATORY DOORS. COOPERATION AND COLLABORATION AMONG RESEARCH GROUPS HAVE ALWAYS BEEN ~~THE~~ HALLMARK OF THE NIH COMMUNITY.

AND WE HAVE AMPLE PROOF OF THE EFFECTIVENESS OF OUR EFFORTS TO FIND, NURTURE, AND SUSTAIN OUR CREATIVE PEOPLE. FOR EXAMPLE, OUR OWN INTRAMURAL NOBEL LAUREATES AND OTHERS WHO HOLD MAJOR SCIENTIFIC HONORS. THE SCIENTISTS WHO TRAINED HERE--SUCH AS MICHAEL BROWN AND JOE GOLDSTEIN--WHO WENT ON TO BECOME LEADERS IN SCIENCE AT OTHER INSTITUTIONS.

I COULD GO ON AND ON CITING THE OUTSTANDING WORK DONE HERE, AND I WOULD PROBABLY BEGIN WITH THE ROSTER FOR TODAY'S PROGRAM. IT IS MOST GRATIFYING TO SEE THAT THE EXCELLENCE IS CURRENT, AND NOT MERELY PAST ACCOMPLISHMENT.

TODAY'S PROGRAM HAS BEEN DEVELOPED BY DR. ABNER NOTKINS AND HIS COMMITTEE SPECIFICALLY TO ENCOURAGE SCIENTISTS FROM ALL PARTS



OF THE INTRAMURAL PROGRAM TO MEET, EXCHANGE IDEAS, AND DISCOVER AREAS OF MUTUAL SCIENTIFIC INTEREST. I SEE TODAY'S ACTIVITY AS THE QUINTESSENCE OF THE NIH INTRAMURAL PROGRAM, A CONCENTRATED VERSION--PERHAPS A BIT MORE FORMALIZED--OF WHAT NIH INTRAMURAL SCIENTISTS DO EVERY DAY AS A PART OF THEIR SCIENTIFIC OCCUPATION. I AM SURE THAT THIS EVENT WILL BE STIMULATING AND LONG REMEMBERED.

227

## FISCAL FUTURE OF BIOMEDICAL RESEARCH\*

by

James B. Wyngaarden, M.D.\*\*

Persons who have made a career commitment to biomedical research have a stake in its fiscal future that transcends their personal financial interests. Under current circumstances the individual scientist's opportunity for achievement and career satisfaction is almost completely bound up with the financial health of research institutions.

Inasmuch as NIH alone funds well over a third of the health research and development performed in the United States, it seems reasonable to project an opinion about the future of all health research and development on the basis of the outlook for the NIH. And despite current fiscal pressures it is my conviction that the road ahead for the National Institutes of Health is promising. My reason for this optimism is the demonstrated commitment of the Federal Government to the support of biomedical research for the improvement of human health—a commitment that is strong and steady in both the executive and legislative branches of our government.

As a starting point for a brief review of the current situation, I will cite some overall statistics on the funding of biomedical research. The total national expenditures for health research and development during 1985 were estimated at \$13.5 billion. The Federal Government supplied just over half of that total or \$6.9 billion. The NIH was the source of \$4.8 billion or over 35 percent of funding for health research and development in the Nation.

---

\*Opening remarks at the Workshop for Medical Staff  
Fellows, NIH Stone House, Bethesda, Maryland,  
September 25, 1986.

\*\*Director, National Institutes of Health, Bethesda, Maryland

Industry's participation in health R & D has increased comparatively in recent years. Ten years ago industry's expenditures amounted to 27 percent of the national total as compared with the current 37 percent, which is slightly more than the NIH share. This recent growth of industry's share reflects in large part the new biotechnology industry, itself an outgrowth of work largely supported by NIH. But about 90 percent of industry's expenditures are for applied work and product development and only 10 percent for basic research, whereas at NIH 90 percent of expenditures are for basic and clinical research and only 10 percent or less for development.

Along with increased expenditures new kinds of relationships have been established by industrial organizations with many academic institutions, including some of the best known and finest. In considering this new trend toward closer cooperation of industry and academia, I have been interested to note the many ingenious contractual arrangements that have been devised to serve optimally the purposes of the partners while protecting their interests with respect to freedom of inquiry, open scientific communications, and proprietary rights.

I am sure that you have been reminded that NIH will shortly begin celebrating a "century of science for health." While there is much of interest and significance in the early history of the Institution, the NIH as we know it today came into being in the aftermath of World War II. Prior to the war almost all of its research had been in-house. After 1945 the partnerships that had been established with universities, medical schools, hospitals, and other research institutions in the war effort were continued and greatly strengthened. Currently about 88 percent of NIH funds are committed to the administration and funding of grants and contracts for research and training carried out in our partner institutions--medical centers, hospitals, universities and research laboratories throughout the Nation.

With only a few exceptions, the annual NIH budget has increased each year since 1945. For a part of that period, from the mid-forties until 1968, the increases were spectacular. The budget grew, during that time,

at the astounding annual rate of 24 percent per year in purchasing power. Since 1968 the growth rate has averaged about 2 percent per year above inflation. Having reached the billion dollar level in the late '60s, however, it would have been surprising if not impossible for the earlier growth rate to be sustained.

Following a brief pause in 1968 the budget resumed a steady climb, though at a slower rate than in previous years. Impetus for continued growth was supplied in part by the interest on the part of both the President and the Congress in launching a "war on cancer." Between 1971 and 1973 the current dollar budget of the National Cancer Institute more than doubled, and by 1975 it had tripled. The National Heart, Lung, and Blood Institute also experienced a period of rapid growth. The budgets of both the NCI and the NHLBI grew faster than the overall NIH budget in the early and mid-1970s, but by the end of the decade the growth differentials among institutes generally disappeared.

Beginning in the early 1970s and continuing to the present, it became necessary to make shifts among the mechanisms used to fund research. Priority was given to research project grants because the number of excellent grant proposals was increasing much more rapidly than the funds available for their support. In 1972 the total number of projects supported was 10,290. By 1985 the number had grown to 18,219. To fund this number of investigator-initiated projects it was necessary to reduce the support for research contracts and research training. Even so, we can only fund about 37 percent of meritorious proposals at this time.

The primary challenge has been to maximize scientific productivity in the face of budgetary limitations. The response has been a continuing series of adjustments in the agency's programs and activities. Such adjustments inevitably translate to hard choices as to priority among competing programs and extend to the difficult choices that must be made between individual grant proposals at the project level.

In constructing the 1987 budget, for example, we were required to make a number of unwelcome choices in program priorities in order to stay within



permitted total levels. As previously we opted to do everything possible to protect funding for investigator-initiated grants. The amounts necessary to maintain our commitment to project grants required that 57 percent of our total FY 87 budget be devoted to that object. I will have a bit more to say about the 1987 budget in a moment.

In recent years when budgets have been especially tight, we have been asked if the NIH intramural program has been subjected to the same budget restraints as those imposed on the extramural program. The answer is yes. From year to year the increases in the two overall programs may differ, favoring first one and then the other, but their growth has been almost exactly the same if compared on a multiyear basis. For example, the growth in the extramural budget between 1977 and 1985 was 114 percent; in the same period the intramural budget grew by 111 percent.

In conclusion I will review briefly the current status of the NIH appropriation for Fiscal Year 1987--which begins in less than a week.

The House has passed, by a vote of 328 to 86, a FY 1987 appropriation bill that would increase the NIH budget by 17 percent over the current budget to a total of \$6.15 billion.

The Senate passed the NIH appropriation by a vote of 83-2. The total approved, \$6.12 billion, was slightly less than the House amount. Inasmuch as the appropriation as passed by the Senate differs from the House version, a conference committee will be required. But either of these appropriation marks would represent about 7 percent real growth in 1987 over the original 1986 appropriation, and a continuation of the trend that began in 1982 when our appropriation was \$3.7 billion. The proposed '87 appropriation is \$2.435 billion or about 66 percent above the '82 level. That represents a real growth rate of about 8 percent per year--rather encouraging I would say, at a time when there is wide perception that biological science isn't receiving the support it warrants.

But there is uncertainty as to what the two Houses will agree upon as the appropriation for NIH for 1987, as well as the possibility that the President may not concur and that his veto be sustained. Furthermore, it is not known at this time what will be the effect of the anti-deficit measures, particularly Gramm-Rudman. But the Congress and the Administration are earnestly working to construct an appropriation and revenue balance that will make draconian anti-deficit measures unnecessary.

In addition to differences in the total amounts appropriated, the Senate and House bills differ on several issues of interest to the NIH and to grantee institutions. The Senate Committee report makes a point of emphasizing a balance in the types of mechanisms used to support research programs, in essence placing emphasis on other programs as well as on research project grants; for example, centers and research training. The House bill had mandated no fewer than 6,200 new and competing renewal grants. Both Houses restored the Biomedical Research Support Grant, which had been recommended for elimination in the President's budget proposal. The question of a limitation on indirect costs was not addressed in the Senate bill, and the House indicated that sufficient funds were included to pay "full direct and indirect costs" of grants.

You may be sure that we will be following closely the progress of the NIH budget.

At the beginning of this discussion I told of my optimism about the future of the National Institutes of Health, and spoke of the commitment to biomedical research of both the legislative and executive branches of the Federal Government. In addition to these champions within the Government, we have many strong advocates outside the Government who act on their conviction of the long-term value of research, and participate to build the case in public testimony before the Appropriations Subcommittees that deal with the NIH budget.

Even the Heritage Foundation, not noted for encouraging Federal expenditures, sounded the same fundamental note that has motivated the establishment and growth of NIH. In a proposal by the staff of the

Heritage Foundation for the FY 1987 Federal budget, titled "Slashing the Deficit," the programs of many agencies were examined in detail. Along with a cautionary note as to how NIH might allocate funds more judiciously, the Foundation staff commented, "Basic biomedical research is one of the few activities funded through Washington which is appropriately a Federal responsibility." The writer continued, "Historically, the benefits of such research have outstripped the taxpayers' cost." I could not have said it better.

I will be happy to respond to any questions you may wish to ask.

224

# SUPPORT OF BIOMEDICAL RESEARCH IN THE LATE 1980'S\*

by

James B. Wyngaarden, M.D.\*\*

It was with pleasure indeed that I accepted a long standing invitation from my friend Dr. Norman Talal to come to San Antonio, and I am delighted to have this opportunity to visit and speak at the University of Texas Health Science Center. First he asked me to give an address on a policy issue. As time went by, he asked me for a title. At one point I suggested something along the lines of "Support of Biomedical Research and Gramm-Rudman," but then I thought about the geography of the situation and decided on "Support of Biomedical Research in the Late 1980s." I will speak generally about the challenges and opportunities that lie ahead for biomedical research in the United States in the closing years of the 1980s.

In my discussion I will speak principally of the National Institutes of Health, but inasmuch as NIH funds well over a third of the health related research in the United States, it seems reasonable to project from it the outlook for biomedical research in our country. Because I am an optimist about the future of the NIH, I view the future of biomedical research with optimism. Despite current fiscal pressures, it is my conviction that the road ahead for the National Institutes of Health is promising. I base this belief on the commitment of the Federal Government to the support of biomedical research for the improvement of human health--a commitment that is steady and strong in both the executive and legislative branches.

Before discussing in some detail the programs of the National Institutes of Health, I will sketch in broad outline some pertinent facts about the research enterprise in the United States.

---

\*Address presented at the Clinical Immunology Research Conference, University of Texas Health Science Center, San Antonio, September 26, 1986.

\*\*Director, National Institutes of Health, Bethesda, Maryland



- The total national expenditures for health research and development during 1985 were estimated at \$13.5 billion. The Federal Government was the source of just over one-half of the total or about \$6.8 billion. The NIH expended \$4.8 billion, or over 35 percent of funding for health research and development in the Nation.

Industry's participation in health R & D has increased comparatively in recent years. For example, ten years ago industry's expenditures amounted to 27 percent of the national total as compared with the current 37 percent, which is slightly more than the NIH share. This recent growth of industry's share reflects in large part the new biotechnology industry, itself an outgrowth of work largely supported by NIH. But about 90 percent of industry's expenditures are for applied work and product development and only 10 percent for basic research, whereas at NIH 90 percent of expenditures are for basic and clinical research and only 10 percent or less for development.

Along with increased expenditures new kinds of relationships have been established by industrial organizations with many academic institutions, including some of the best known and finest. In considering this new trend toward closer cooperation of industry and academia, I have been interested to note the many ingenious contractual arrangements that have been devised to serve optimally the purposes of the partners while protecting their interests with respect to freedom of inquiry, open scientific communications, and proprietary rights.

The NIH has a deep and continuing interest in such arrangements but has no intention of intervening in them.

#### NIH Since 1945

- The NIH shortly will begin observance of its centennial, celebrating "a century of science for health." There are many fascinating stories of human courage and of brilliant scientific achievement in the institution's history. For today's discussion, however, I will

confine historical references to budgetary trends and policy developments of the past 40 years.

- The period since the end of World War II is the era of the modern NIH--the agency as we know it today. Prior to the War, almost all of its research had been in-house. After 1945 the partnerships that had been established with universities, medical schools, hospitals, and other research institutions in the war effort were continued and, in fact, strengthened. Currently about 88 percent of NIH funds are committed to extramural research and training.
- With only a few exceptions, the annual NIH budget has increased each year since 1945. For a part of that time, until 1968, the increases were spectacular. From 1945 to 1968 the budget grew at an astounding average rate of 24 percent per year in purchasing power.  
(Slides 1a, 1b)

#### Adjusting to Deceleration in Budget Growth

- By 1970, due largely to the budget stresses of the Vietnam war, the NIH appropriation took at least one step backward. Some saw the reduction as the "beginning of the end of Federal support for biomedical research." It was, in fact, the "end of the beginning." Even so, the NIH budget has not since then been reduced from one year to the next.
- The growth rate since 1968 has averaged about 2 percent per year in purchasing power. (Slide 2)
- By 1970 a well-planned initiative led to the "war on cancer" with the President and the Congress vying for the leadership in providing funds and organizational innovations for the conquest of cancer. Between 1971 and 1973 the budget of the National Cancer Institute more than doubled in current dollars. It had tripled by 1975.

- The National Heart, Lung, and Blood Institute also experienced a period of rapid growth, increasing by 54 percent between 1971 and 1973, and doubling by 1977.
- The budgets of both NCI and NHLBI grew faster than the total NIH budget during the early and mid '70s. By the end of the decade, however, the growth differentials generally disappeared.
- Beginning in the early 1970s and continuing to the present, another set of program adjustments has taken place involving shifts among the mechanisms used for funding research. Priority was given to research project grants with a concomitant reduction in budget for research contracts and research training. (Slide 3)

#### Priority for Project Grants and Heightened Competition

- The total number of project grants supported in 1972 was 10,290, by 1985 the total had grown to 18,219. In this period the average award per project remained virtually unchanged in constant dollars. The average in current dollars, however, increased from \$59,000 in 1972 to \$147,000 in 1985. (Slide 4) But indirect costs took an increasing share of the research award, rising from 21 percent in 1972 to 31.3 percent in 1985. (Slide 5) Consequently, the average real support available per project for direct costs was reduced, or at best was unchanged.
- The progress of science has resulted in an increased number of grant proposals. A total of 18,675 competing research grant applications were reviewed in 1985. In 1976 the total was 10,050, and in 1971 less than 8,000. (Slide 6)
- We have become increasingly concerned about maintaining a relatively stable and predictable level of new and competing renewal grants. The number of competing awards fluctuated widely over the past decade, from a low of 3,464 in FY 1976 to a high of 6,247 in FY 1985.

- We made it a major goal of our original "stabilization initiative" to fund at least 5,000 new and competing renewal grants each year atop the moral commitments of some 11,000 continuation grants. In all but 3 of the past 10 years we have awarded at least 5,000 new and competing renewal grants. Budget limitations, however, have precluded a comparable degree of stability for other research and training programs of the NIH.
- However, in spite of the progressive annual shift of funds into research project grants, the number of applications has grown faster than resources.

In 1976 we could fund about 48 percent of grants eligible for award, but in 1984, 1985 and 1986 we were able to fund only about 37 percent. As would be predicted, the paylines are progressively lower.  
(Slides 7, 8)

#### Side Effects of Increased Competition - Stresses on the Peer Review and Awards System

- Another result of fiscal constraints plus increased competition is the increasing frequency with which grant proposals are being resubmitted after unsuccessful competitive review. In 1965, 6 percent of applications reviewed were resubmissions--in 1975, 15 percent were resubmissions, and by 1985 the proportion of resubmissions was about 25 percent of all applications. As might be expected, resubmitted applications enjoy a higher success rate than initial proposals, reflecting heightened influence of the study section on the form and substance of grant applications.
- In response to the tougher competition and the widespread perception that study sections often look for minor flaws or omissions in proposals under review and that small factors shift priority scores, applicants tend to overdocument. As a result, the workload for both the applicant and the study section is greatly increased.



- Although fiscal constraints are responsible for much of the difficulty experienced by the research community, certain attributes of the current extramural award system may be more burdensome than necessary for the investigator, the grantee institution, and the NIH peer review system. In order to increase productivity with the resources available to us, we have instituted several changes in the review and award process.
- In our judgment one of the factors that is contributing needlessly to the workload of both the grant applicant and the NIH peer review system is the excessive complexity and sheer bulk of the research grant application. In addition to proposing page limitations for grant application, we have taken other steps to reduce the reviewing time for study section members as well as preparation time for the applicant.

#### FIRST and MERIT Awards

- We have observed that when the award rate falls the percentage of successful first-time applicants also falls. It is essential to the vitality of the scientific enterprise and to the morale of the scientific community that young scientists be encouraged. We recently announced a new program called FIRST awards (First Independent Research Since Training)—a modification of the R-23s which lengthens the awards from 3 to 5 years and the total to \$350,000 of direct costs for the 5 years. This should obviate the need for too early reapplication for investigators who encounter difficulties in the first 18 months of their grants. It will, we believe, encourage more creative and less defensive research.
- Further, we have expanded the number and types of longer term support for outstanding mid-career scientists through a new program called MERIT awards (Method for Extending Research in Time). This program will involve facilitated extensions of 5-year awards for an additional 3 to 5 years on the basis of a detailed progress report, rather than

though reapplication. (The extension will be tallied as a competing renewal.)

- We believe that a greater number of longer grants to both first-time and established investigators represents an efficient and prudent investment of public funds. However, the budgetary implications in the fourth and fifth years and beyond are substantial, and in the absence of major funding increases could reduce the number on new and competing renewal grants we would be able to make in future years.

#### Research Training and Career Development

- There are two general categories of NIH training programs--those funded through National Research Service Awards (NRSA) and those encompassed in the more advanced career development series.
- Individual fellowships are awarded through national competition under the NRSA. Institutional awards under the NRSA program permit institutional selection of trainees at both the predoctoral and postdoctoral level. The medical science training program, supported through institutions within the NRSA program, is considered to be one of the most successful in an area critically important to the future.
- The 1985 appropriation permitted a substantial increase of stipends in postdoctoral categories making the income for clinical postdoctoral fellows and trainees more compatible with that of house staff. Equity was maintained for the Ph.D. who, after two years of postdoctoral training, is contributing in an important way to research activity. Postdoctoral stipends were increased so that with funds for tuition and other expenses, our total outlay per student per year became essentially the same as that offered by the National Science Foundation.
- Opportunities for advanced research preparation are offered through the NIH Research Career Development Program (K Series). The oldest of these is the Research Career Development Award (RCDA), solely for

salary and fringe benefits. More than 80 percent of those who have received RCDAs now have research project grants. Other K Series awards include the Academic Investigator Award, the Clinical Investigator Award, the Mid Career Development Award, and the Physician/Scientist award. These awards provide a salary of up to \$40,000 plus applicable fringe benefits. The actual salary is intended to be comparable to that of others at the same institution at the same level of training and experience.

- The 1985 appropriation provided over \$217 million for 10,623 NRSA fellows and trainees. The 1986 appropriation (after Gramm-Rudman) is for \$209 million and will support 9,947 NRSA fellows and trainees.

Our budget for career development programs in 1985 was over \$76 million, supporting 1,318 awards. The 1986 budget for career awards is about \$100,000 lower than last year's and provides for 44 fewer awards.

#### Instrumentation, Facilities and Laboratory Animals

- Over the past decade increasing concerns have been expressed regarding obsolescence of research instrumentation and facilities in the nation's research institutions. A study on instrumentation jointly funded by the National Science Foundation and the NIH was completed last year. The report showed a national need for newer equipment in many laboratories, particularly public institutions. The outstanding need seems to center on relatively low-cost instruments in the \$10,000 to \$75,000 range, perhaps reflecting some degree of success in warding off critical needs for large instruments through ongoing NIH programs for sharing such instruments.
- For a number of years the condition of academic research facilities has steadily deteriorated. Federal support in this area has been limited and diminishing. The extent of the need for Federal support of health-related research facilities is difficult to ascertain since no comprehensive assessment of this need has been made since 1968.



- During the past century virtually every major development in biomedical research has depended at some point upon the use of animals. A small but determined segment of society is opposed to the use of animals in research, and they are bringing increasing pressure on scientists, physicians and many institutions staging sit-ins, demonstrations, as well as vandalism, break-ins and bomb threats against investigators and others associated with studies requiring animals.

I am pleased to say that NIH and other defendants earlier this month won a court case that had been brought in the United States Court of Appeals (Fourth Circuit) by three animal rights groups and some individuals. The plaintiffs demanded custody of the well-known Silver Spring monkeys. A judge had put these 15 monkeys in NIH's interim custody after the principal investigator had been charged with animal cruelty—a charge that was later dismissed. The animal rights people asserted that they had standing to sue because they were taxpayers and also helped support the monkeys after the owner gave them up temporarily. They also said they were promoting the humane treatment of animals and that they had a personal relationship with the monkeys.

The language of the Court's decision is worth quoting to you:

"To imply a cause of action in these plaintiffs might entail serious consequences. It might open the use of animals in biomedical research to the hazards and vicissitudes of courtroom litigation. It may draw judges into the supervision and regulation of laboratory research. It might unleash a spate of private law-suits that would impede advances made by medical science in the alleviation of human suffering. To risk consequences of this magnitude in the absence of clear direction from the Congress would be ill-advised. In fact, we are persuaded that Congress intended that the independence of medical research be respected and that administrative enforcement govern the Animal Welfare Act."

We are greatly heartened by this common-sense action by the judges of the Court of Appeals.



Permit me to turn now to the state of the NIH budget for FY 1987.

Appropriations for FY 1987

- The House has passed an appropriation bill for NIH for FY 1987 and the Senate is considering its version which differs slightly from the House measure.

By a vote of 328 to 86 the House passed an appropriation bill that would increase the NIH budget by 17 per cent to a total of about \$6.15 billion.

The Senate passed the NIH Appropriation by a vote of 83-2. The total approved, \$6.12 billion, was slightly less than the House amount. Inasmuch as the appropriation as passed by the Senate differs from the House version, a conference committee will be required. But either of these appropriation marks would represent about 7 percent real growth in 1987 over the original 1986 appropriation, and a continuation of the trend that began in 1982 when our appropriation was \$3.7 billion. The proposed '87 appropriation is \$2.435 billion or about 66 percent above the '82 level. That represents a real growth rate of about 8 percent per year--rather encouraging I would say, at a time when there is widely held perception that biological science isn't receiving the support it warrants.

- But there is uncertainty as to what the two Houses will agree upon as the appropriation for NIH for 1987, as well as the possibility that the President may not concur and that his veto be sustained. Furthermore, it is not known at this time what will be the effect of the anti-deficit measures, particularly Gramm-Rudman. But the Congress and the Administration are earnestly working to construct an appropriation and revenue balance that will make draconian anti-deficit measures unnecessary.
- In addition to differences in the total amounts appropriated, the Senate and House bills differ on several issues of interest to the NIH

and to grantee institutions. The Senate Committee report accompanying the bill made a point of emphasizing a balance in the types of mechanisms used to support research programs, in essence placing emphasis on other programs as well as on research project grants; for example, centers and research training. The House bill had mandated no fewer than 6,200 new and competing renewal grants. Both houses restored the Biomedical Research Support Grant, which had been recommended for elimination in the President's budget proposal. The question of a limitation on indirect costs was not addressed in the Senate bill, and the House indicated that sufficient funds were included to pay "full direct and indirect costs" of grants.

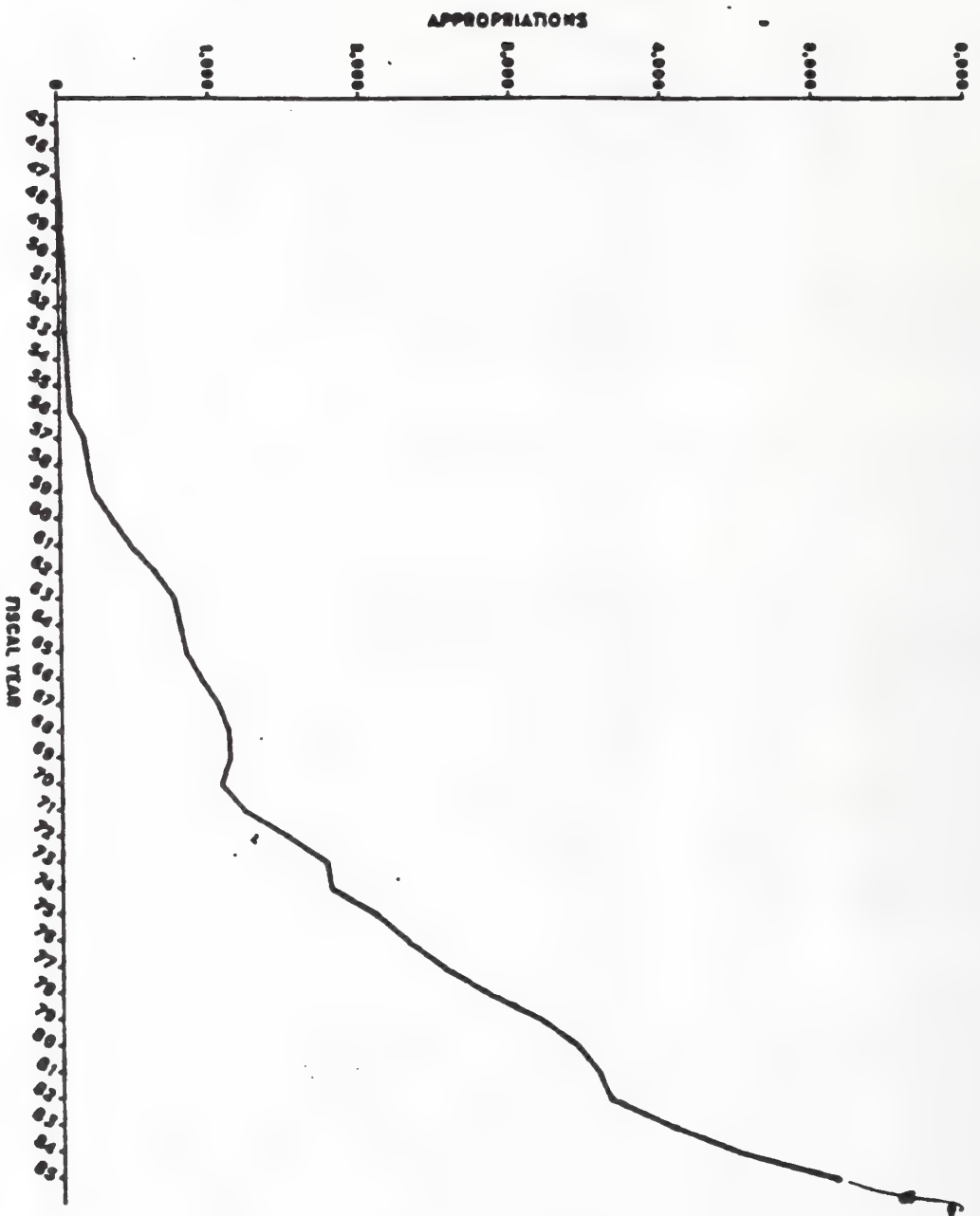
You may be sure that we will be following closely the progress of the NIH budget.

- At the beginning of this discussion I told of my optimism about the future of the National Institutes of Health, and spoke of the commitment to biomedical research of both the legislative and executive branches of the Federal Government. In addition to these champions within the Government, we have many strong advocates outside the Government who act on their conviction of the long-term value of research, and participate to build the case in public testimony before the Appropriations Subcommittees that deal with the NIH budget.

Even the Heritage Foundation, not noted for encouraging Federal expenditures, sounded the same fundamental note that has motivated the establishment and growth of NIH. In a proposal by the staff of the Heritage Foundation for the FY 1987 Federal budget, titled "Slashing the Deficit," the programs of many agencies were examined in detail. Along with a cautionary note as to how NIH might allocate funds more judiciously, the Foundation staff commented, "Basic biomedical research is one of the few activities funded through Washington which is appropriately a Federal responsibility." The writer continued, "Historically, the benefits of such research have outstripped the taxpayers' cost." I could not have said it better.

I will be happy to respond to any questions you may wish to ask.

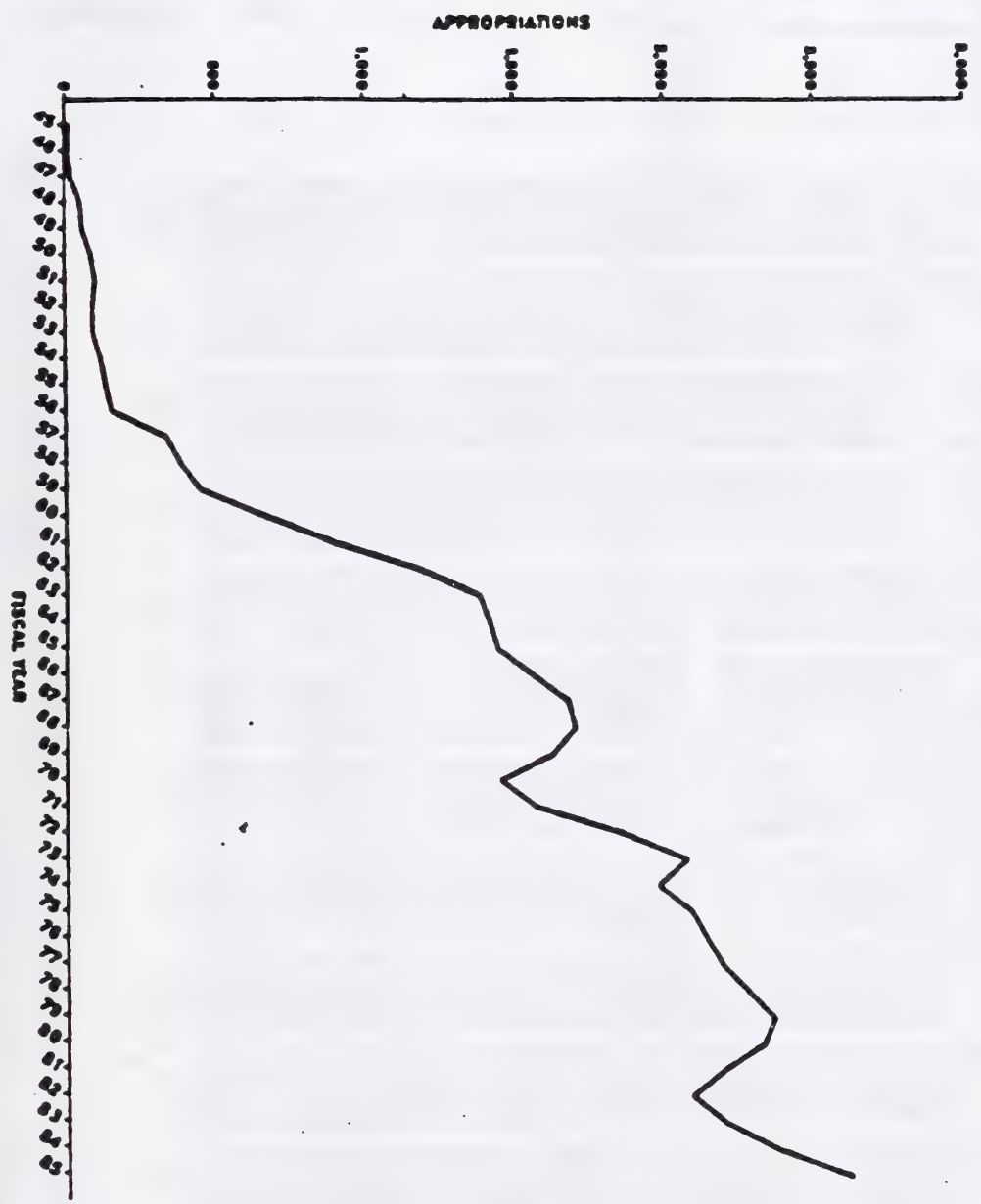
# Total NIH Appropriations in Current Dollars, FY 1945-85 Excluding Programs Transferred Out (Dollars in Millions)



NOTES: TO excluded. 1985 data preliminary.

PAB/DP4/OPPE/00, April 1985

# Total NIH Appropriations in Constant (1975) Dollars, FY 1945-85 Excluding Programs Transferred Out (Dollars in Millions)



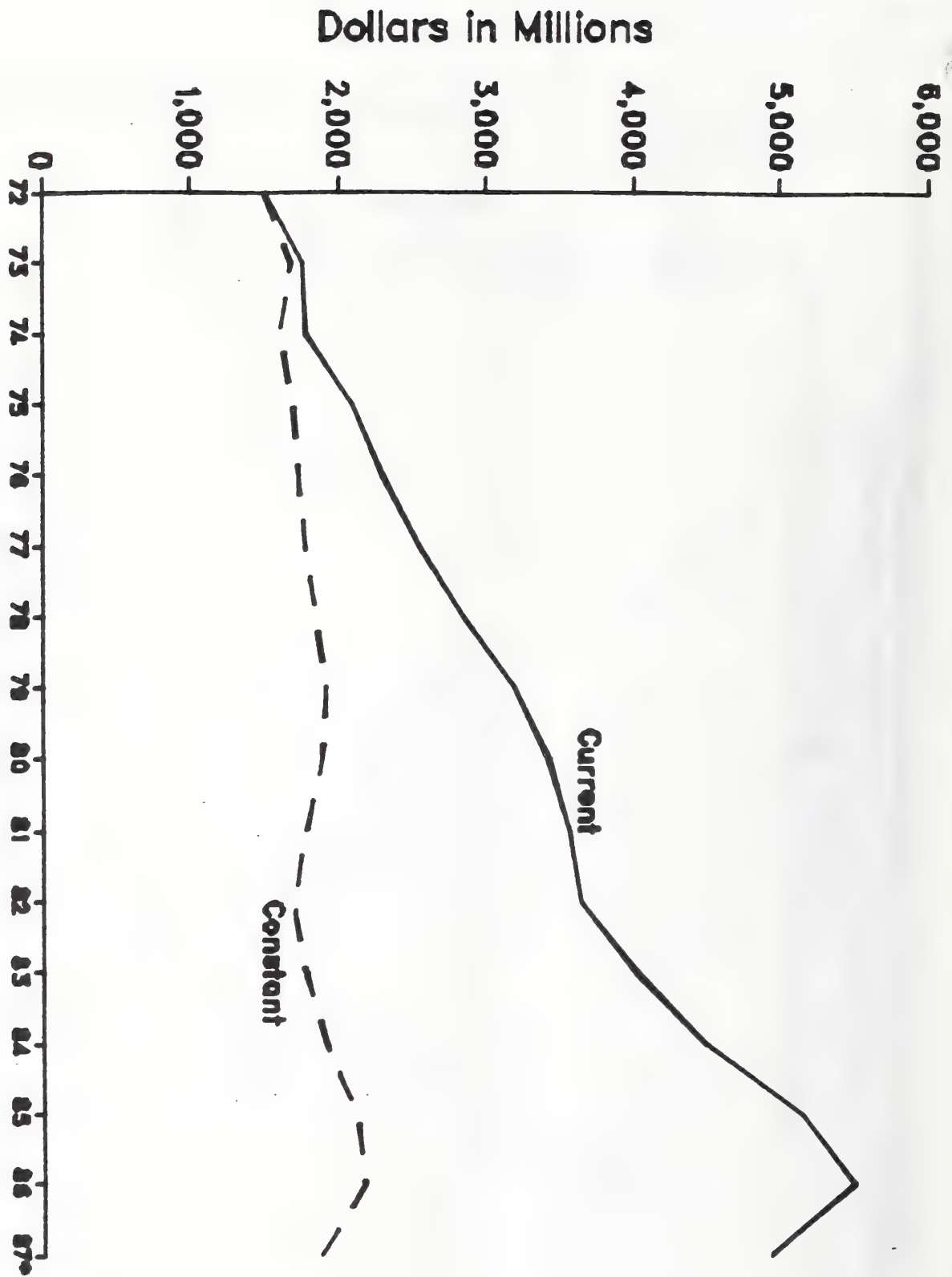
NOTES: Constant dollar conversion uses BODP, 10 excluded, 1985 data preliminary.

PAB/DPA/OPPE/00, April 1985



# Total NIH Appropriations, 1972-80, in Current and Constant Dollars (1972=100)

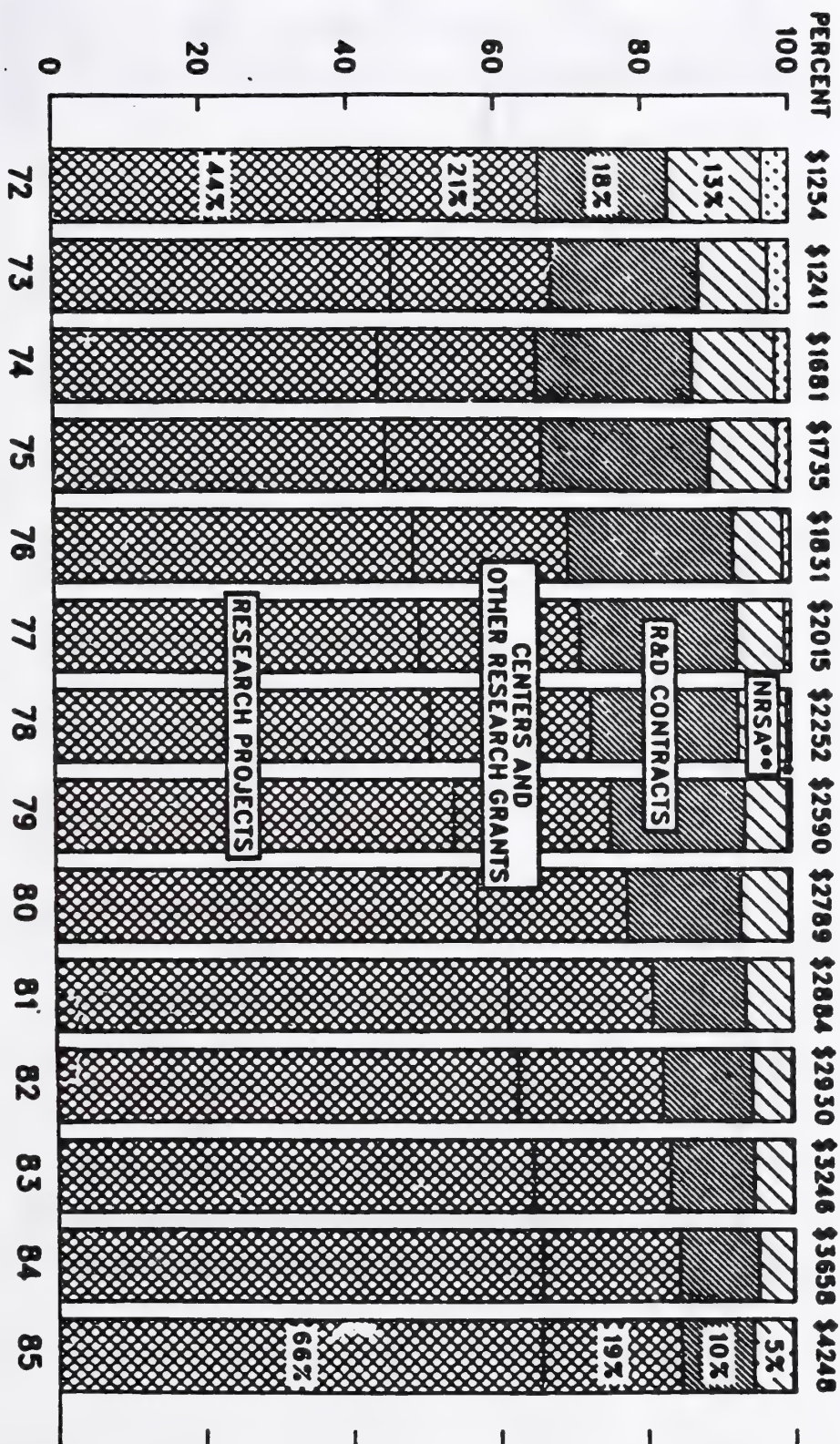
2.



\*=estimated

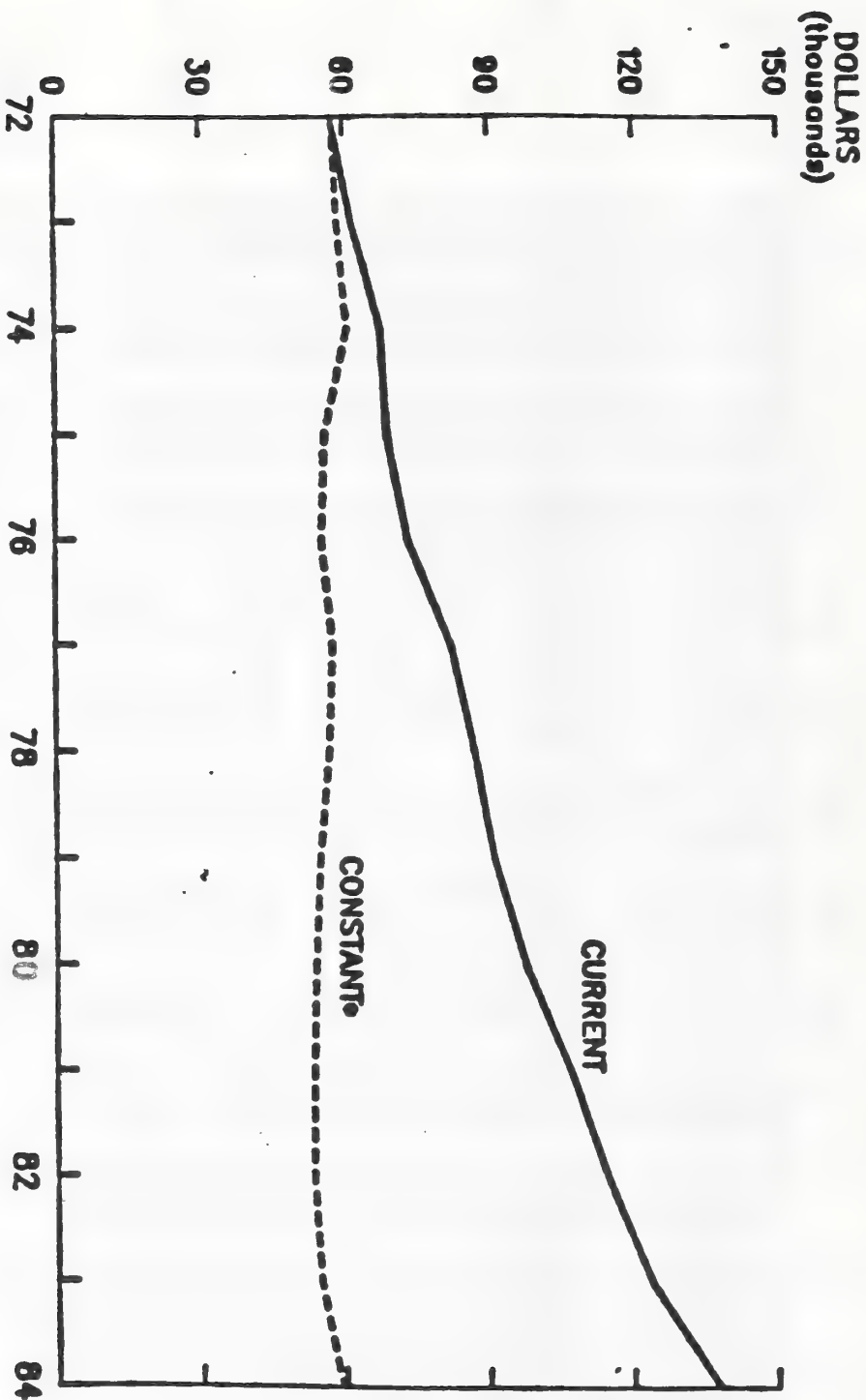
# ALLOCATION OF NIH EXTRAMURAL AWARDS BY ACTIVITY, FISCAL YEARS 1972-1985 PERCENT OF AMOUNT AWARDED (CURRENT DOLLARS IN MILLIONS)

3



NOTE: EXCLUDES TO. \*INCLUDES CONSTRUCTION AND MEDICAL LIBRARY GRANTS. \*\*INCLUDES PRE-NRSA TRAINING.  
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

# AVERAGE DOLLARS FOR NIH RESEARCH PROJECT GRANTS FISCAL YEARS 1972-1984

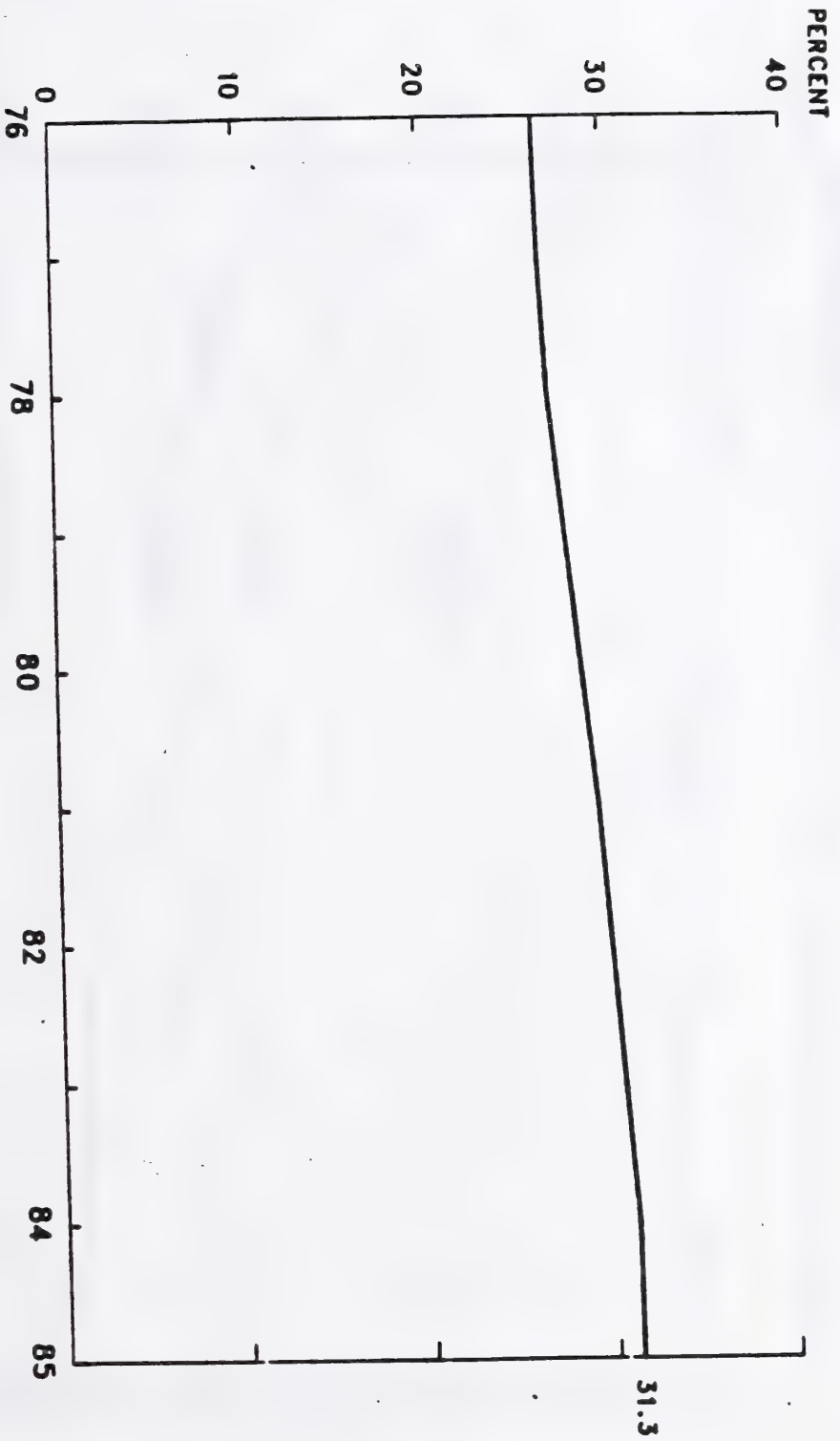


BASED ON BIODIVERSITY AND PRICE INDEX 1972-100.  
SOURCE: NIH, DRO, STATISTICS AND ANALYSIS BRANCH

11/83  
V1/83

INDIRECT COST PROPORTION OF TOTAL COST FOR NIH RESEARCH GRANTS  
FISCAL YEARS 1976-1985

5

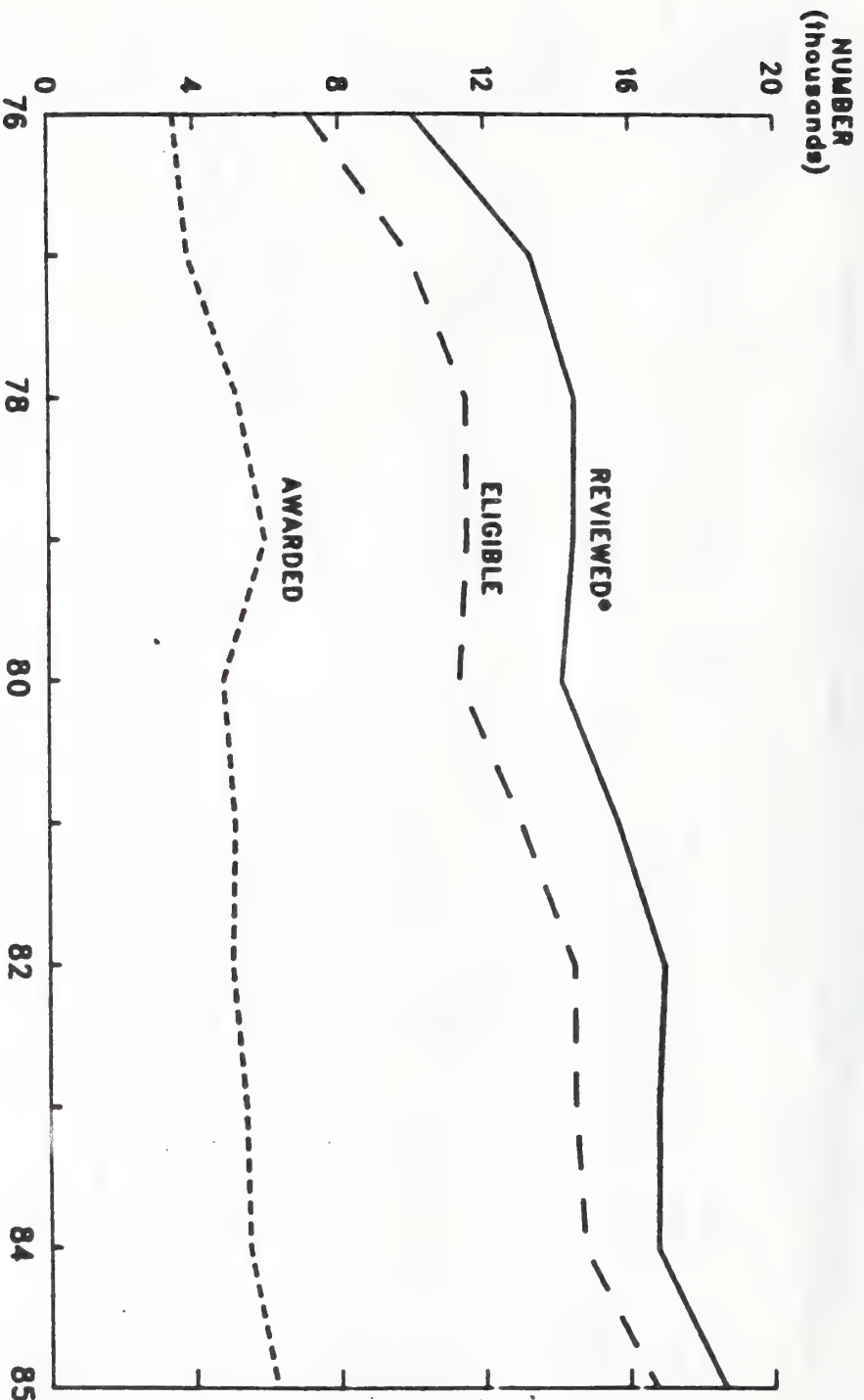


NOTE: EXCLUDES CONFERENCE AND NCI EDUCATION GRANTS, BRD, BRS, RCP AWARDS, AND MINORITY STUDENT APPRENTICE PROGRAMS. EXCLUDES THE TO. SEE TECHNICAL NOTE ON PAGE III FOR ACTIVITY COVERAGE.  
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH



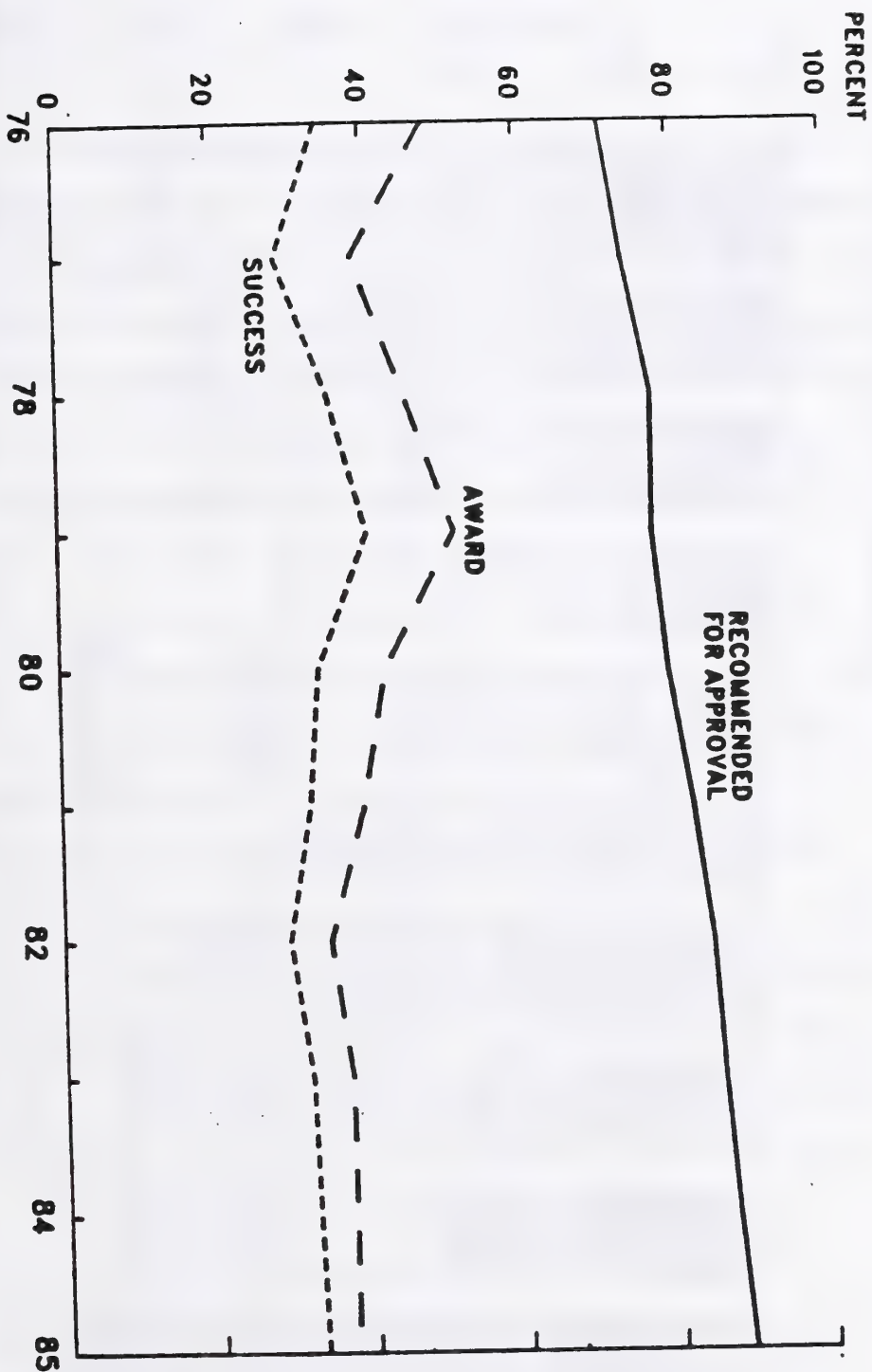
6

# NUMBER OF NIH COMPETING RESEARCH PROJECT APPLICATIONS REVIEWED, ELIGIBLE AND AWARDED, FISCAL YEARS 1976-1985



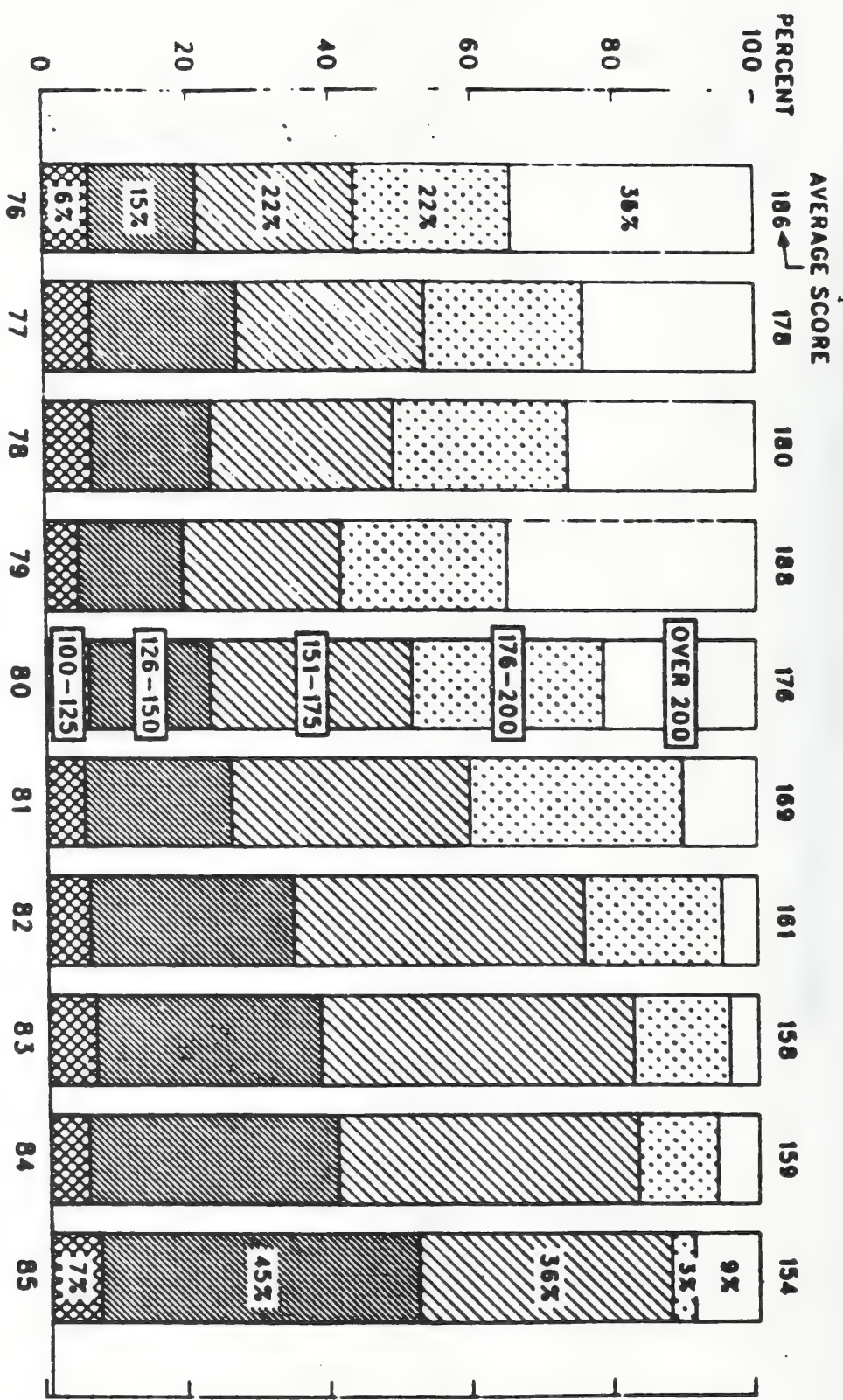
NOTE: EXCLUDES 10. SEE TECHNICAL NOTE ON PAGE III FOR ACTIVITY COVERAGE AND PROCEDURES.  
REPORTING YEAR.  
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

COUNCIL RECOMMENDED FOR APPROVAL, AWARD, AND SUCCESS RATES  
FOR NUMBER OF NIH RESEARCH PROJECT APPLICATIONS  
FISCAL YEARS 1976-1985



NOTE: EXCLUDES 10. SEE TECHNICAL NOTE ON PAGE III FOR ACTIVITY COVERAGE.  
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

DISTRIBUTION OF NUMBER OF NIH COMPETING RESEARCH PROJECTS AWARDED  
BY PRIORITY SCORE GROUP, FISCAL YEARS 1976-1985



NOTE: BASED ON ACTUAL SCORES. EXCLUDES TQ.  
SEE TECHNICAL NOTE ON PAGE III FOR ACTIVITY COVERAGE.  
SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

INTRODUCTORY REMARKS\*

BY

JAMES B. WYNGAARDEN\*\*

I am pleased to be able to welcome you to this important meeting on behalf of the World Health Organization, the European Medical Research Council, and the National Institutes of Health. I am particularly happy to note that the momentum generated at the first meeting in 1981, which was strengthened at the 1985 meeting, has not diminished. In fact, additional experts--from the communications professions--will augment our discussions today and tomorrow.

It is very appropriate that a full two days has been set aside for consideration of information transfer in technology assessment. NIH has always had--as a part of its research mission--a strong commitment to communicating biomedical information. Dr. Itzhak Jacoby will talk in more detail later about NIH's activities in communicating information in the direct context of technology assessment. We have also devoted major resources to communicating other forms of scientific information to the medical community primarily through meetings, seminars,

---

\*Presentation at the Joint Meeting of the World Health Organization, European Medical Research Council and the National Institutes of Health, Copenhagen, Denmark, October 7, 1986

\*\*Director, National Institutes of Health, Bethesda, Maryland



and workshops and through journal publication. Our National Library of Medicine is positioned at the frontier in finding ways to improve access to the vast and growing store of scientific information. Some of you may be familiar with special, computerized communications such as PDQ--the Physician Data Query system--whereby practicing physicians with personal computers can gain immediate access to data banks containing the latest information on cancer treatment protocols.

For communicating with the public, of course, we have employed direct means such as pamphlets and brochures and, in certain crucial areas, free telephone lines. The mass media--newspapers, magazines and the broadcast channels--are for us another important aspect of communicating scientific information to the general public.

With regard to information transfer relating specifically to technology assessment, we are faced with a difficult paradox: while the channels to the medical community and to the public are well in place, our job becomes more difficult by virtue of the sheer volume of data being sent into the channels.

. . .

In my view, these meetings on technology assessment have not diminished in urgency since 1981. If the experience of the United States is any guide, we can expect that as the cost of

health care continues to grow and make up a larger percentage of the Gross National Product, pressure will increase worldwide for examination of the roles that biomedical technologies in general and specific medical technologies in particular play in macroeconomics.

As all of you know, the NIH is the primary Federal agency in the U.S. responsible for support and conduct of the spectrum of biomedical research, from basic to applied studies.

Over the years, the American public, through the U.S. Congress, has been extremely supportive of the Federal efforts in biomedical research. For many years, NIH Directors could stand before appropriations committees and make the case for additional research funding by reviewing the research advances that had already had an impact on improving the health of the Nation, and forecasting what we might expect in the future in terms of reductions in mortality and morbidity. The implicit promise that our efforts would eventually help people was often enough to assure budget increases for research.

More and more often in recent years, however, I am pressed with questions about the payoffs of biomedical research in economic terms. I am frequently asked to justify our mission in terms of its impact upon the economy. This is a formidable task, and even the best econometric studies are complicated by such

factors as the difficulties in separating the contributions of basic and applied research in biomedicine, in distinguishing the separate contributions of public and private investments in biomedical research and development, and in assigning improvements in health to specific innovations.

Clearly, biomedical research continues to fuel technology, which in turn seems to be offering up more and more advances with direct application in the health care setting, at what seems to be an ever-increasing pace. This phenomenon raises concerns about the possible impact of biomedical research upon the cost of health care.

In an attempt to gather some data to counter the general view that research advances tend to drive up the cost of health care, I recently asked the various NIH components to provide some examples of recent advances in biomedical research that have reduced health care costs. Although we must consider many of the examples they raised as estimates--based on necessary assumptions--a sample of just 12 amounted to about \$2.5 billion in savings annually. Some of the cost savings stemmed directly from biomedical advances subsequently applied to medical practice. For example, research in sheep supported by NIH in years past implicated prostaglandins in maintaining the patency of the ductus arteriosus. This has led to treatment of newborns

with the patent ductus syndrome using the prostaglandin synthetase inhibitor, indomethacin--a therapy successful in about 85% of cases. We estimate that indomethacin as a substitute for surgical treatment now saves approximately \$180 million annually in the U.S. And the research leading up to this clinical advance cost only about \$10 million! Other similar examples stemming directly from biomedical research include use of antenatal steroid therapy in high risk pregnancies to prevent respiratory distress syndrome--estimated to save about \$295 million annually--and use of laser treatment for several blinding conditions--estimated to save about \$150 million annually.

Other savings stem directly from technology assessment studies. For example, an NIH-supported study of coronary artery disease has shown that management of certain cases through medical care and drugs rather than surgery could save about \$500 million annually in the United States. Similarly, another NIH-supported study showed that a widely used neurosurgical procedure to prevent stroke or stroke death --extracranial/intracranial bypasses-- is no more effective than aspirin and standard hypertension control. The conclusions of the study are being followed widely, and very few EC/IC bypasses are now performed in the United States, thus saving at least \$30 million annually.



No one to date has suggested seriously that we curtail biomedical research in order to contain rising health care costs. But, I think we are left with a number of challenges: First, to increase the effectiveness of our intervention and second to continue research that will bring us beyond the highly expensive halfway point in treatment of diseases and up to the point where we know enough to make important contributions to disease prevention. In addition, it is important, to develop data more useful in convincing those who make decisions about spending for biomedical research, that research also ultimately contributes to cost savings in health care.

Clearly, diligent efforts in technology assessment, followed by dissemination of the results of those assessments, plus sound policy decisions are crucial undertakings. If technology in medicine must be controlled, surely it is better that it be managed closer to the "application" end of the spectrum than at the knowledge acquisition end. To cripple biomedical research in any way in an effort to cut health care costs would be shortsighted at best.

In closing, permit me to use the familiar quotation from Lewis Thomas, in which he added "halfway technology" to our lexicon and stated a truth about which we need to be reminded periodically. Here are his words: "I say that we must continue doing biomedical research on about the same scale and scope as in

the past 20 years with expansion and growth of the enterprise being dependent on where new leads seem to be taking us. It is an expensive undertaking....but it is still nothing like as expensive as trying to live with the halfway technologies we are obligated to depend on in medicine today: if we are to try to stay with these for the rest of the century, the cost will go through the ionosphere."

Cognizant of the impact technology assessment will have on the many facets of health care and, perhaps, upon how biomedical research is viewed within this context, I wish you a most successful conference.



## CURRENT STATUS OF TREATMENT OF GENETIC DISEASE\*

by

James B. Wyngaarden, M.D.\*\*

The planners of this symposium have wisely limited the expanse of the topic to be discussed. I thought it might be useful to define the scope of the problem in general terms.

Genetics is concerned with the study of hereditary variations. Most of these variations are not harmful, indeed many confer a distinct biological advantage by enabling the species to adapt to changing environments. But when variations are extreme and impair the health, fitness, or reproductive capacity of the individual, we consider them diseases. Such variations are of three principal types: chromosomal aberrations, single gene differences that exhibit mendelian patterns of inheritance, and polygenic disorders in which two or more genes, indeed often multiple genes, contribute to the characteristic in question. We will be considering only the second class of hereditary disorders, namely those that are attributable to single gene differences, and within that group discussion will largely concern a small subset, the inborn errors of metabolism.

In the 1983 edition of his catalogue on mendelian inheritance in man, Victor McKusick<sup>1</sup> lists phenotypic variations of 1637 established genetic loci, thus implying that at least that many genes have undergone mutation so as to cause human disease or polymorphism. The gene product is known in only about 15 percent of the mendelian disorders that have been recognized on clinical grounds. We now know of over 200 different instances in which a deficiency or abnormality of a specific enzyme has been associated with an hereditary disease. There are perhaps another 40 examples of deficiency states involving circulating proteins that are not usually considered enzymes, although some such as the clotting factors may also be. In this listing, the multiple

---

\*Presented at the Institute of Medicine Annual Meeting in Washington, D.C., on October 15, 1986.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



variants of enzymes such as glucose 6-phosphatase dehydrogenase or of the non-enzyme proteins such as the abnormal hemoglobins are counted once each. Thus there are about 250 hereditary diseases in which we have a fairly clear understanding of pathogenesis.<sup>2</sup>

In a recent sampling of the effects of mendelian disease on human health, Costa, Schriver, and Childs<sup>3</sup> found that 76 percent of Mendelian phenotypes were disadaptive, causing impairment, disability, or handicap, and causing a measurable impact on lifespan, reproductive capacity, and psycho-social characteristics. They found that 25 percent of the disadaptive mendelian phenotypes were apparent at birth and over 90 percent by the end of puberty. They found that 58 percent of phenotypes involved more than one anatomical or functional system and that lifespan was reduced in 51 percent, reproductive capacity in 69 percent, and that most phenotypes compatible with life beyond infancy caused psycho-social handicap and limited access to schooling and to work.

Individually, monogenetic disorders are rare, but as a group they affect at least 1 percent of live-born infants. They account for nearly 10 percent of admissions to pediatric hospitals in North America, 8 1/2 percent of child deaths, and 7 percent of stillborn and neonatal deaths.<sup>3</sup> Thus the collective burden of genetic disease is enormous, with a disproportional, although by no means exclusive, impact upon the very young. In their recent review of response to treatment of patients with mendelian diseases, Hayes, Costa, Schriver, and Childs<sup>4</sup> found that treatment provided limited benefit to lifespan, reproductive capacity, and social adaptation for the diseases in their sample. Treatment expanded lifespan to normal in only 15 percent of those diseases in which longevity was reduced in the untreated state. There was some improvement in lifespan in about 45 percent and in the final 40 percent there was no apparent extension of lifespan at all. The improvements in lifespan, reproduction, and social adaptation were greater in diseases of known pathogenesis where specific approaches to therapy based upon biochemical insights were possible.

Inborn errors of metabolism are genetic diseases attributable to specific absent or defective enzymes and a disturbance of a specific biochemical reaction. There are a few examples known in which the genetic mutation affects an enzyme in such a manner that it is more active than the native enzyme

because of an increase in its intrinsic specific activity, an increased affinity for one of its substrates, or a decreased susceptibility to normal inhibitors and regulators. In such circumstances an excessive amount of reaction product is formed. In one such example an excessive activity of an enzyme catalyzing an early rate limiting step in purine nucleotide synthesis results in flamboyant overproduction of uric acid, and severe gout and uric acid kidney stones in young men. But this condition is an exception and the vast majority of inborn errors of metabolism result in a diminished or blocked reaction in some pathway. When this occurs the normal product of that reaction will be diminished, and if the block is complete and there are no other reactions forming the same substance, the deficiency of product may be total.

One example of such a lesion is the species-wide absence in man, other primates, and guinea pigs of the enzyme that synthesizes ascorbic acid, vitamin C. Thus scurvy might be viewed as an inborn error of man held in permanent abeyance by the frequent ingestion of ascorbic acid. Although not many examples of replacement therapy are as uniformly successful as this one, the principle of supplying the missing product is utilized in several other inborn errors of metabolism. For example, in the adreno-genital syndrome, a defect in steroid transformation results in reduced synthesis of hydrocortisone, and excessive by-product production of androgens. Administration of a glucocorticoid supplies the missing product, and suppresses the excessive production of androgens by way of the pituitary. Also there are several examples of metabolic cretinism that result from specific defects in formation of the iodo-thyronine ring or of the insertion of iodine into it in the thyroid gland. The administration of the missing product, thyroxine or one of its derivatives, corrects the cretinism, and if begun sufficiently early may also avert the abnormalities of intellectual development. Replacement therapy can, of course, also be used in compensating for the lack of adequate formation of certain nonenzymic proteins, such as the administration of gamma-globulin in agamma globulinemia, of albumin in analbuminemia, or of factor VIII in hemophilia.

In another large class of inborn errors it is the accumulation of the substrate behind the blocked reaction that leads to a disease state. In certain of these instances, dietary restriction may reduce the accumulation burden of the critical substrate. An early and still important example is

phenylketonuria in which the absent or deficient activity of phenylalanine hydroxylase results in accumulation of phenylalanine in body fluids, and excessive production of toxic phenylketone products. Routine neonatal screening now detects the majority of affected infants and the early institution of an appropriately restricted diet converts this condition to a non-disease for most patients. Nevertheless a recent study by Koch and associates<sup>5</sup> shows that the collective I.Q. of patients treated from birth is not quite up to that of their non-PKU siblings, and that if treatment is stopped in childhood the collective I.Q. falls significantly. Galactosemia is another example of a disease in which the accumulation of a substrate of a blocked reaction proves toxic, resulting in brain damage, cataracts, and general failure to thrive. Early diagnosis and dietary avoidance of galactose are remarkably successful in most, but Komrower<sup>6</sup> pointed out in 1982 that a significant fraction of galactosemic patients have prenatal manifestations that are not reversed by post-natal therapy. Other examples in which dietary restrictions help to ameliorate the effects of hereditary disease include restriction of fructose intake in children with fructose-1-phosphate-aldolase deficiency, and restriction of protein in children with enzymic defects of the urea cycle that lead to ammonia intoxication, principally those due to argininosuccinic aciduria and citrullinemia.

Many inborn errors of metabolism are the result of absence of key enzymes involved in the metabolic degradation of complex molecules. Such defects may result in progressive intra-cellular and extra-cellular storage of substances that are minimally water soluble. Several of the glycogen storage diseases fall into this category, as do the mucopolysaccharidoses, such as Hurler's and Hunter's disease, and lipid storage diseases such as Gaucher's disease and Tay-Sachs disease. Several of these are devastating illnesses and produce extensive distortion of tissues, serious intellectual impairment, neurological disease and early death. In several, including Gaucher's disease, Tay-Sachs disease, Pompe's disease or glycogen storage disease type 1, attempts have been made to replace the missing protein in the form of highly purified enzymes, but the biochemical effects (if any) have been transient, and clinical improvement not discernible. Nevertheless, there have been some successes in the pharmacological depletion of substances stored to excess because of inborn errors of metabolism. Examples that come to mind include the depletion of excess copper from patients with Wilson's Disease, of excess iron in



hemachromatosis, of uric acid in gout with uricosuric agents, and of cholesterol in familial hypercholesterolemia with cholestyramine.

Sometimes it is possible to counter the metabolic error with the use of a metabolic inhibitor. Allopurinol reduces uric acid production in gout by inhibiting xanthine oxidase thereby allowing the more soluble hypoxanthine to become a substitute end product for some of the uric acid. Another example is the use of clofibrate in Type 3 hyperliproteinemia with reduction of plasma triglyceride levels due to reduced glyceride synthesis or release in the liver.

The final group of pharmacological therapies of importance in a limited number of diseases concerns agents that alter deficient enzyme activity and increase it into a therapeutically useful range. One example is homocystinuria, in which about half of subjects have a mutant form of cystathionine  $\beta$ -synthase enzyme with reduced affinity for its cofactor, pyridoxine. Administration of fairly large doses of pyridoxine increases cystathionine  $\beta$ -synthase activity with partial or complete correction of homocystinuria and reduction of the risk of vascular thromboses. Another splendid example involves disorders of propionic and methylmalonic acid metabolism in which the inborn error involves not the substrates themselves but the biotransformation of precursor forms of vitamin B-12 into active cofactors. In appropriately selected children with defects of adenosyl cobalamine synthesis, cobalamine supplements distinctly improve the developmental prognosis even though the biochemical defect is not totally corrected and methylmalonic aciduria persists. Finally, there is the use of phenobarbital to treat children with the Crigler-Najjar syndrome type 2, a neonatal jaundice condition in which the hepatic enzyme bilirubin UDP glucuronyl transferase is reduced but not absent. Phenobarbital acts as a liver microsomal enzyme inducer, and children with this syndrome treated with phenobarbital show reductions in degrees of hyperbilirubinemia.

A number of inborn errors of metabolism affect renal function and may give rise to life-threatening renal failure. Renal transplantation has been successfully employed in several such situations, for example in treatment of renal failure due to Alport's syndrome, renal amyloidosis, cystinosis, Fabry's disease, and oxalosis. In virtually all instances transplantation has been employed as treatment for end stage renal failure, and not primarily for enzyme replacement. Nevertheless, in some circumstances there has been general



amelioration of the systemic disease, and in Fabry's Disease for example there have been measurable serum levels of ceramide tri-hexosidase following renal transplantation. In certain instances the underlying hereditary disease has resulted in reaccumulation of deposits in the kidney. This is most strikingly the case in oxalosis in which the immediate reaccumulation of oxalate deposits in the kidney leads to rapid functional failure of the transplant.

Liver transplantation has also been used in treatment of organ failure in certain hereditary diseases. The largest experience has been in children with alpha-1-antitrypsin deficiency or Wilson's disease hepatic failure. The results have generally been good, in fact in Wilson's disease there appears to be some amelioration of extrahepatic components of the disorder. Tyrosinemia, Glycogen's Storage disease type I, and hemophilia A are other conditions in which hepatic transplantation has been successfully employed.

Fifty or more cardiac transplantations have been performed for hereditary cardiomyopathies, and the two and five year survivals for this group are at least as good as those for cardiac transplants in general.

Finally there is the important topic of marrow transplantation for immuno-deficiency states, such as the Wiskott Aldrich syndrome or severe combined immunodeficiency disease. In both of these conditions there has been a substantial number of long term survivals, ten years or more, without "recurrence" of the disease. The results for severe combined immunodeficiency disease due to adenosine deaminase deficiency have been very satisfactory in the 30 percent of the cases in which allogeneic marrow transplantation was possible.<sup>7</sup>

In summary, I have tried to make several points in this short paper. One is to emphasize the immense collective burden of genetic disease. Another is to point out the limited success of current strategies for dealing with these diseases as a group. The third is that in certain highly specific instances a great deal can be accomplished, and in fact in the review by Hayes and colleagues,<sup>4</sup> treatment completely corrected the disease impact in 12 percent of the sample and provided a partial response in another 40 percent of cases, although in about one half of the latter cases the response was rather poor. In those instances in which treatment was effective, the normal gene product could successfully be delivered to its normal site of action or environmental manipulation restored homeostasis. Treatment was less effective when the

disorder involved complex metabolic systems such as glycolysis, energy metabolism, or structures critical for development.

Experience during the last 30 or more years employing diverse strategies thus points out some of the extraordinary challenges facing new strategies. These include earliest possible detection and treatment, for which intrauterine intervention would be required in many instances. Also one would need to provide the missing product or remove accumulated toxic substrates before structural or developmental damage had occurred. If the goal is administration of replacement enzymes, these would need to be given in protected form, and conveyed to the appropriate intracellular sites where their actions were critical. This is a daunting challenge but it is being addressed with the use of carrier particles coated with enzyme that it is hoped will be taken up by lysosomes in the case of missing lysosomal enzyme diseases, or with the use of purified enzymes protected with covering side groups to compound proteolytic systems.

Where existing strategies have been successful, there is every reason to continue their use. But in the large the success of conventional strategies has been limited, and clearly new ones are needed for a range of devastating diseases for which there is at present no successful ameliorative or curative approach. And that brings us to the topic of human gene transplantation for somatic cell defects, a discussion of candidate conditions, the state of science in the field, and the ethical issues and public expectations engendered by these prospects.

1. McKusick VA. Mendelian inheritance in man: catalogs of autosomal dominant, autosomal recessive, and X-linked phenotypes" (6th Ed.), Johns Hopkins University Press, Baltimore, 1983.
2. Stanbury JB, Wyngaarden JB, Fredrickson DS, Goldstein JL, Brown MS. Inborn errors of metabolism in the 1980s. In The Metabolic Basis of Inherited Disease (5th Ed.), McGraw-Hill, New York, 1983.
3. Costa TM, Scriver CR, Childs B. The effect of Mendelian disease on human health. I: A measurement. Am J Med Genet 21: 231-242, 1985.
4. Hayes A, Costa TM, Scriver CR, Childs B. The effect of Mendelian disease on human health. II: Response to treatment. Am J Med Genet 21: 243-255, 1985.

5. Koch R, Azen C, Friedman EG, Williamson ML. Paired comparisons between early treated PKU children and their matched sibling controls on intelligence and school achievement test results at eight years of age. J Inherited Metab Dis 7: 86-90, 1984.
6. Komrower GH. Galactosaemia--thirty years on: the experience of a generation. J Inherited Metab Dis 5: (Suppl 2) 96-104, 1982.
7. Parkman R. The application of bone marrow transplantation to the treatment of genetic diseases. Science 232: 1373-1378, 1986.

## BACKGROUND AND PURPOSE OF CENTENNIAL OBSERVANCE\*

BY

JAMES B. WYNGAARDEN, M.D.\*\*

MANY PEOPLE WHO ARE REASONABLY WELL ACQUAINTED WITH THE NIH FIND IT HARD TO BELIEVE THAT WE ARE APPROACHING OUR 100TH BIRTHDAY. MOST WOULD DATE OUR BEGINNING AS SOMETIME AROUND WORLD WAR II. THAT PERSPECTIVE, HOWEVER, FAILS TO CONSIDER A RICH AND PRODUCTIVE ERA IN THE AGENCY'S HISTORY. A NUMBER OF THE EVENTS AND PROMINENT PERSONS OF THE FIRST 50 YEARS WILL BE MENTIONED IN LATER PARTS OF TODAY'S PROGRAM, SO RATHER THAN PRESENTING A CHRONOLOGY AT THIS TIME, I WILL REFER TO A FEW HIGHLIGHTS AS REMINDERS OF SOME OF THE CRITICAL EPISODES IN OUR HISTORY--DEVELOPMENTS WHOSE OUTCOMES SHAPED THE FUTURE COURSE OF THE INSTITUTION.

ONE SUCH EVENT WAS THE MOVE OF THE HYGIENIC LABORATORY TO WASHINGTON IN 1891. THIS MOVE UNDERScoreD THE STATUS OF THE LABORATORY AS A NATIONAL RESOURCE. AT FIRST THE FACILITY WAS LOCATED IN THE BUTLER BUILDING NEAR THE CAPITOL, BUT IN 1904 THE LABORATORY WAS MOVED INTO NEWLY CONSTRUCTED BUILDINGS THAT WERE DESIGNED FOR RESEARCH ACTIVITIES. THE LABORATORY AT 25TH AND E STREETS WAS THE INSTITUTION'S HOME FOR NEARLY 35 YEARS. IT WAS

---

\*ADDRESS PRESENTED AT THE OPENING CEREMONY OF THE NIH CENTENNIAL OBSERVANCE, MASUR AUDITORIUM, OCTOBER 16, 1986.

\*\*DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND



THE SITE OF MANY HEROIC AND SUCCESSFUL BATTLES AGAINST DISEASE LED BY SUCH GIANTS AS DRS. HOWARD TAYLOR RICKETTS AND JOSEPH GOLDBERGER.

DURING THIS PERIOD THE CONGRESS ENACTED THE RANSDELL ACT OF 1930, A LANDMARK IN OUR HISTORY. IT CHANGED THE NAME OF THE HYGIENIC LABORATORY TO THE NATIONAL INSTITUTE OF HEALTH, AND EXPANDED ITS EMPHASIS FROM CONCENTRATION ON INFECTIOUS DISEASES TO THE BROADER MISSION OF "ASCERTAINING THE CAUSE, PREVENTION AND CURE OF DISEASE."

AMONG THE EVENTS HAVING A SUBSTANTIAL IMPACT ON THE FUTURE OF NIH WAS THE GIFT OF LAND BY THE WILSONS--THE GENEROUS AND UNUSUAL ACT TO WHICH I MADE REFERENCE EARLIER IN THE PROGRAM.

ANOTHER LANDMARK EVENT IN THE HISTORY OF NIH TOOK PLACE AT THE END OF WORLD WAR II WHEN THE OFFICE OF SCIENTIFIC RESEARCH AND DEVELOPMENT, GOING OUT OF EXISTENCE, TURNED OVER FUNDS TO BE USED AS GRANTS TO COMPLETE SOME 250 RESEARCH PROJECTS IN PROGRESS AT UNIVERSITIES, MEDICAL SCHOOLS, AND PHARMACEUTICAL COMPANIES. THE HIGH-LEVEL DECISION TO TRANSFER THE GRANTS TO NIH NOT ONLY CONFIRMED ITS ROLE AS THE PRINCIPAL BIOMEDICAL RESEARCH ARM OF THE FEDERAL GOVERNMENT, IT ALSO ESTABLISHED EXTRAMURAL GRANTS AS A POWERFUL MECHANISM FOR THE SUPPORT OF SUCH RESEARCH.

ALTHOUGH THAT TRANSFER OF FUNDS INVOLVED LESS THAN ONE MILLION DOLLARS, THE EVENT MARKED THE BEGINNING OF THE MODERN NIH THAT CURRENTLY FUNDS SOME 20,000 GRANTS AT AN ANNUAL COST OF ALMOST \$4 BILLION.

OTHER EVENTS CRUCIAL TO THE GROWTH OF NIH TO AN ANNUAL BUDGET OF WELL OVER \$5 BILLION WILL BE MENTIONED LATER IN THE PROGRAM.

I WOULD LIKE TO TURN BRIEFLY TO THE OBJECTIVES OF THE CENTENNIAL OBSERVANCE THAT OFFICIALLY BEGINS TODAY.

FIRST, WE PLAN TO IMPROVE THE PUBLIC'S UNDERSTANDING OF THE WORTH AND BENEFIT OF BIOMEDICAL RESEARCH--OF THE ESSENTIAL ROLES PLAYED BY THE PARTNERS IN DISCOVERY--ACADEMIA, THE PRIVATE SECTOR, AND THE FEDERAL GOVERNMENT. THE CENTENNIAL GIVES AN OPPORTUNITY TO REMIND A PUBLIC THAT HAS FORGOTTEN OR NEVER KNEW WHAT THE WORLD WAS LIKE BEFORE THE ADVANCES OF MODERN MEDICINE. THE YEAR OF 1887 IS A LONG WAY AWAY IN THE CONTEXT OF HUMAN HEALTH. WE CAN REMIND THE PUBLIC OF HOW FAR WE HAVE COME.

SECONDLY, WE CAN USE THE OBSERVANCE AS AN EFFECTIVE MECHANISM IN OUR EFFORTS TO ATTRACT MORE YOUNG, BRIGHT PEOPLE INTO THE ADVENTURE THAT IS BIOMEDICAL RESEARCH. WE ARE BEGINNING TO REALIZE THE AWESOME POTENTIAL OF MODERN RESEARCH TECHNIQUES, BUT WE NEED TO REMIND YOUNG PEOPLE PARTICULARLY OF HOW FAR WE HAVE TO GO.

IN OUR ENDEAVOR TO MEET THESE OBJECTIVES, WE HAVE PLANNED A SUBSTANTIAL NUMBER AND VARIETY OF ACTIVITIES, MANY OF WHICH WOULD NOT BE POSSIBLE WERE IT NOT FOR THE PROMPT AND GENEROUS SUPPORT FROM ORGANIZATIONS AND INDIVIDUALS OUTSIDE THE GOVERNMENT.

LATER IN TODAY'S PROGRAM I WILL TELL YOU OF SOME OF THE PRINCIPAL CENTENNIAL PROJECTS.

ADVISORY COMMITTEE TO THE DIRECTOR, NIH

Minutes of the 54th Meeting  
October 16-17, 1986

The Advisory Committee to the Director, NIH, held its 54th meeting on October 16-17, 1986, at the National Institutes of Health, Bethesda, Maryland. Dr. James B. Wyngaarden, Director, chaired the meeting. (See attachment for agenda and lists of participants.)

FIRST DAY

Introductory Remarks

Dr. James B. Wyngaarden  
Director, National Institutes of Health

Dr. Wyngaarden began by expressing his appreciation that many of those present had participated that morning in the ceremony to open NIH's year-long observance of its centennial. He noted that the centennial observance has two objectives: (1) to educate the public about the health benefits that have resulted from biomedical research during the past 100 years, and (2) to stimulate the interest of young people in biomedical research careers. In addition, Dr. Wyngaarden invited everyone to participate in the events scheduled during the year at NIH and at various academic centers throughout the United States.

Turning to the subject for discussion--a project to characterize the entire human genome by chromosome mapping and DNA sequencing techniques--Dr. Wyngaarden pointed out that its long-standing commitment to understanding the genetic basis of human development and disease inevitably involves NIH in this effort. For example, NIH sponsors many resources, such as GenBank®, BIONET, the Human DNA Probe Repository, and the Human Genetic Mutant Cell Repository, that will be essential to any mapping and sequencing efforts. In fact, the current feasibility of such a project results from pioneering basic research in genetics, biochemistry, and cell biology that has been supported by NIH for many years.

The overriding questions are whether the likely benefits to human health outweigh the costs of a concerted mapping and sequencing effort and, thus, whether NIH should support such an effort at this time, especially if support requires a reduction in other research activities. Despite considerable debate (and the creation of the term genomics to describe this field), there is as yet no consensus among scientists about how such a project should proceed or even whether it should proceed beyond the traditional approach of locating and sequencing genes of identified biological interest.

The potential benefits of mapping and sequencing the human genome seem compelling. In particular, the new information resulting from this effort



would certainly improve the ability to diagnose and understand human disease. Recently, for example, Dr. Stuart Orkin applied a form of "reverse genetics" in cloning a gene of unknown function by using the knowledge of its probable location on a genetic map that he had gained through a study of gene rearrangements associated with chronic granulomatosis. Possession of a map of the entire human genome would expand the utility of this technique dramatically. Furthermore, both the map and the sequence would have important additional benefits in the study of normal human function and development, drug development, agriculture, and other areas in biology.

On the other hand, these potential benefits must be weighed against some very real concerns. The effort would be expensive and time-consuming, possibly compromising other excellent research initiatives. For example, estimates of the cost of simply sequencing the human genome range from less than 100 million to a few billion dollars and the benefits would not be immediate. Coordination of the project among laboratories, among agencies, and among countries would be difficult but necessary to avoid duplication and to ensure that data are freely and easily accessible to all.

Concluding his introductory remarks, Dr. Wyngaarden presented the chairman of the first session, Dr. George Palade.

#### State of the Science

Dr. George E. Palade, Session Chairman  
Senior Research Scientist of Cell Biology  
School of Medicine, Yale University

Dr. Palade began by describing the dimensions of the effort involved in the contemplated sequencing of the entire human genome in terms of two separate calculations:

1. The number of human genes already mapped is approximately 1,000; the ratio of mapped to unmapped genes is at least 1:50.
2. The total calculated number of nucleotides in the human genome is about 3 billion; the ratio of sequenced to unsequenced nucleotides is approximately 1:600.

Given these two ratios, the dimensions of the unknown are clearly vast enough to elicit curiosity. Therefore, Dr. Palade observed, the primary question--should scientists sequence the human genome--is probably going to be answered in the positive.

Several practical issues regarding preparedness, procedures, and organization must be addressed before such an initiative is undertaken, however. It is also necessary to keep in mind that the end result of this project would be only a starting point, founded on a composite set of chromosomes. The degree of reliability and usefulness of this baseline must be proved by sequencing genomes from other sources.

WELCOMING REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

Less than a week ago we held a formal ceremony in this auditorium that was the first official event in the year-long observance of the centennial of the National Institutes of Health. Over the next 12 months there will be centennial seminars, conferences, receptions, dinners--a variety of events here and in many places in the United States, as well as in other countries, giving public recognition to the role of the National Institutes of Health in the "century of science for health." We view the centennial as an opportunity to focus public attention on the significant progress of biomedical science in the past 100 years. The story of that progress is a story not only of the NIH but also of its partners in the biomedical research enterprise: universities, the private sector, and voluntary and professional organizations. We believe that in the events, programs, publications and productions saluting the centennial, important messages will be conveyed--such as the fact that biomedical research has brought about many of the medical advances we enjoy today and is essential to assure health improvements for the future. Another is a message mostly for young people that a biomedical research career offers an exciting and a challenging opportunity to improve the health and wellbeing of current and future generations.

I wish to make special mention of two centennial events. The culmination of the observance will take place in mid-October next year. Three outstanding symposia are being planned to be held in connection with a reunion of NIH alumni--the scientists and science administrators from across the world who at some time in their careers were researchers or officials at the National Institutes of Health. I hope that any alumni

---

\*Presented at the NIAMS/NAAB conference on "Molecular Biology: Its Potential for Advancing Rheumatology Research," Masur Auditorium, Bethesda, Maryland, October 20, 1986.

\*\*Director, National Institutes of Health, Bethesda, Maryland

here today will reserve October 15-18, 1987, and make plans to attend the symposia and reunion. Another important event in the fall of 1987 will be the broadcast on PBS of a four-part program now being produced that will tell of the extraordinary advances of the health-related sciences during the past century, and will illustrate the key part that has been played by the NIH in those advances.

As a matter of fact, this conference itself has been designated by the National Institute of Arthritis and Musculoskeletal and Skin Diseases as a part of its observance of the NIH birthday year. The conference is also the first major event to be sponsored by the NIAMS, our newest institute, now not even halfway through its first year.

The central theme of this conference is an illustration of much that is happening in the biosciences today. Progress in molecular biology is so rapid as to be a virtual explosion. It is responsible for many of the advances in the past decade that have revolutionized biomedical research.

In the course of the presentations and discussions to follow, the participants will assess what impact such advances have had on research related to the rheumatic diseases and, more important, what potential progress might be made by more rapidly focusing such new techniques toward rheumatic disease research. Because the most rapidly breaking research area involves the use of molecular biology and recombinant DNA techniques, this area will be emphasized.

For the next two days leading scholars of selected major rheumatic diseases will review and discuss, as background, current knowledge and concepts of the pathogenesis of these diseases, indicating the areas of major gaps in knowledge that could profitably be addressed by applying this new biotechnology. Leading investigators already utilizing such techniques for the study of rheumatic diseases also will describe their current research as well as potential applications for future directions.

The sponsors have also brought together a group of world renowned experts in gene cloning and molecular and cell biology who have done



formative research in areas related to rheumatic diseases. These investigators will present a series of state-of-the-art lectures designed to inform and instruct about the power of these new methodologies and how they have already been applied to begin unraveling the mysteries of the human gene in health and disease. In addition, several renowned molecular biologists, not currently involved in the study of rheumatic diseases, will discuss potential applications of such techniques to rheumatic diseases.

Under the auspices of both the National Arthritis Advisory Board and the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the planners of this program developed this conference to present these modern technologies and advances especially to new investigators, research associates, fellows, and physician scientists.

The organizers have told me that they feel enormously fortunate in having assembled this distinguished faculty and anticipate that the individual lectures and other interactions will catalyze future research and career development of young investigators in this area. Applied molecular biology is at the forefront of research advances and presents challenges for the academic medical community to focus this enormously powerful discipline on questions related to human disease and its management. We look forward to an educational and inspiring conference, and I am pleased on behalf of the NIH to extend a warm welcome to each of you.





KEYNOTE ADDRESS\*

BY

JAMES B. WYNGAARDEN\*\*

I AM VERY HAPPY TO BE HERE TODAY TO OPEN THIS SESSION OF THE MEETING. ALL OF US IN THE HEALTH COMMUNITY WORLDWIDE SHARE CONCERNS ABOUT THE SOCIAL CONSEQUENCES OF THE APPLICATION OF HIGH TECHNOLOGY FOR THE DIAGNOSIS AND TREATMENT OF DISEASE AND THE IMPACT OF THESE POWERFUL INSTRUMENTS ON COST, AVAILABILITY, AND EFFICACY OF HEALTH CARE. EARLIER THIS MONTH I ATTENDED A MEETING IN COPENHAGEN SPONSORED BY THE NIH, THE WORLD HEALTH ORGANIZATION AND THE EUROPEAN MEDICAL RESEARCH COUNCIL ON TECHNOLOGY ASSESSMENT. WHILE THAT MEETING FOCUSED ON METHODOLOGIES FOR TECHNOLOGY ASSESSMENT AND INFORMATION TRANSFER, THE IMPETUS BEHIND THAT SESSION AND THIS ONE IS SIMILAR.

THE PRACTICE OF MEDICINE HAS BECOME INCREASINGLY BASED IN TECHNOLOGICAL DEVELOPMENTS OVER THE PAST 50 YEARS. BEGINNING IN THE MIDDLE 1930S, WITH THE DISCOVERY OF SULFONAMIDES, IT BECAME POSSIBLE FOR PHYSICIANS TO INTERVENE IN SUCH A MANNER AS TO ALTER THE NATURAL HISTORY OF LARGE GROUPS OF DISEASES. THE BIRTH OF

---

\*PRESENTED AT THE FOURTH INTERNATIONAL CONGRESS ON THE IMPACT OF NEW IMAGING TECHNOLOGY ON HEALTH CARE, RESEARCH, AND TEACHING, SAN FRANCISCO, CALIFORNIA, OCTOBER 24, 1986.

\*\*DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND

MODERN MEDICINE IS OFTEN ASSIGNED TO THAT DATE. THE TREND HAS CONTINUED AND THE PACE HAS QUICKENED. CURRENTLY THE DISCOVERIES IN MOLECULAR BIOLOGY AND IMMUNOLOGY SEEM TO BE DRIVING THE FIELD. POWERFUL NEW TECHNOLOGIES FOR THE DIAGNOSIS AND TREATMENT OF DISEASE ARE BEING ANNOUNCED WITH REGULARITY. AMONG THE MOST SPECTACULAR ADVANCES ARE THOSE ASSOCIATED WITH IMAGING--TECHNIQUES MADE POSSIBLE BY THE EXTRAORDINARY LEAPS OF UNDERSTANDING THAT HAVE TAKEN PLACE IN ELECTRONICS, THE COMPUTER SCIENCES, PHYSICS, MOLECULAR BIOLOGY, AND PHYSIOLOGY.

IN REFLECTING ON THE ORIGINS OF THESE TECHNIQUES, ONE IS STRUCK BY THE CONVERGENCE OF DISCIPLINES THAT IS INCREASINGLY EVIDENT IN HIGHER TECHNOLOGY. ONE CANNOT HELP BUT BE IMPRESSED BY THE BRILLIANT AND CREATIVE WORK OF SCIENTISTS AND ENGINEERS IN MANY FIELDS WHO HAVE BROUGHT US TO THIS POINT. I AM ALSO REMINDED THAT WITHIN THE BIOMEDICAL SCIENTIFIC ENTERPRISE ITSELF DURING THE RECENT YEARS, THERE HAS BEEN A CONVERGENCE HAVING PROFOUND IMPLICATIONS. NOBEL LAUREATE ARTHUR KORNBERG RECENTLY CALLED ATTENTION TO THE "CONFLUENCE OF THE MANY DISCRETE AND PREVIOUSLY UNRELATED MEDICAL SUBJECTS INTO A SINGLE UNIFIED DISCIPLINE." HE OBSERVED THAT "ANATOMY, PHYSIOLOGY, BIOCHEMISTRY, MICROBIOLOGY, IMMUNOLOGY, AND GENETICS HAVE NOW BEEN MERGED AND ARE EXPRESSED IN A COMMON LANGUAGE OF CHEMISTRY." THAT IS ALSO TRUE, IT SEEMS, IN THE FIELD OF MEDICAL IMAGING.

BUT ALL OF US KNOW THAT EVEN THOUGH THE ASTONISHING TOOLS THAT WILL BE DISCUSSED HERE ARE OF RECENT ORIGIN, THEY DID NOT SUDDENLY EMERGE FULLY DEVELOPED.

IN WRITING ABOUT THE EXCITING TIME IN MEDICAL HISTORY WHEN ANTIBIOTICS WERE DISCOVERED, LEWIS THOMAS REMINDED THAT "IT NEEDS EMPHASIZING THAT IT TOOK ABOUT 50 YEARS OF CONCENTRATED EFFORT IN BASIC RESEARCH TO REACH THIS LEVEL," AND "IF THIS RESEARCH HAD NOT BEEN DONE, WE COULD NOT HAVE GUESSED THAT STREPTOCOCCI AND PNEUMOCOCCI EXIST AND THE SEARCH FOR ANTIBIOTICS WOULD HAVE MADE NO SENSE AT ALL."

THE DISTINGUISHED BRITISH PHYSICIAN AND SCIENTIST, SIR HAROLD HIMSWORTH, EXPRESSED THE SAME THOUGHT IN SOMEWHAT DIFFERENT WORDS IN A LECTURE PUBLISHED IN 1973. HE SAID THAT "WHEN FUTURE HISTORIANS LOOK BACK AT THE PERIOD IN WHICH WE ARE NOW LIVING, THEY ARE LIKELY TO SEE IT AS THAT TIME IN WHICH SCIENTIFIC KNOWLEDGE EMERGED FROM ITS ADOLESCENCE TO BECOME A MAJOR FACTOR IN THE AFFAIRS OF HUMAN SOCIETIES."

THE PROGRESS IN THE LAST TWO GENERATIONS IN THE APPLICATION OF SCIENCE TO HEALTH HAS STIMULATED EXPECTATIONS. PEOPLE TODAY ARE BEING TAUGHT TO EXPECT GOOD HEALTH CARE. IN THE PAST, THROUGHOUT HISTORY, MAN HAS TENDED TO ACCEPT ILLNESS, PLAGUES, AND PERSONAL INJURY AS "NORMAL." THIS IS NO LONGER THE CASE. THE NEWFOUND ABILITY OF MEDICINE TO CONTROL OR EVEN TO ERADICATE



234  
DISEASE--A DIRECT LEGACY OF RESEARCH--HAS BROUGHT INTO BEING NEW HUMAN EXPECTATIONS AND EVEN DEMANDS. THERE IS AMPLE EVIDENCE THAT MOST PATIENTS WANT THE MOST EFFECTIVE TREATMENT, NOT THE LEAST COSTLY TREATMENT. INEVITABLY, SUCH A DEVELOPMENT HAS MAJOR ECONOMIC IMPLICATIONS.

THE COMPLEX CALCULUS OF COST-BENEFIT ANALYSIS OF MEDICAL PROGRESS IS ILLUSTRATED IN AN EXAMPLE CITED 20 YEARS AGO BY DR. LOWELL COGGESHALL, THEN VICE PRESIDENT FOR MEDICAL AFFAIRS OF THE UNIVERSITY OF CHICAGO. WRITING IN A REPORT ON MEDICAL EDUCATION, HE COMPARED COSTS OF THE OLD AND NEW MEDICINE. "ONCE," HE SAID, "IT TOOK ONLY ONE DOCTOR TO RESIGN HIMSELF AND THE CHILD'S PARENTS TO THE INEVITABLE DEATH OF A BLUE BABY; IT NOW TAKES A TEAM OF MEDICAL SPECIALISTS AND AUXILIARY PERSONNEL TO CORRECT THE CONGENITAL ABNORMALITY OF A BABY'S HEART TO INSURE THE CHILD A NORMAL LIFESPAN. MORE THAN 100 MEDICAL SPECIALISTS, NURSES, AND SKILLED TECHNICIANS ARE INVOLVED IN PREPARATIONS FOR AND PERFORMANCE OF THE OPERATION AND IN THE POSTSURGICAL CARE OF THE PATIENT."

IN THE COURSE OF SEEKING FUNDS FOR THE RESEARCH ENTERPRISE, PERSONS IN POSITIONS LIKE MINE ARE CONSTANTLY BEING CALLED UPON TO JUSTIFY THE PURPOSES OF THE SUBSTANTIAL INVESTMENT REQUIRED. IN JUSTIFYING TO THE CONGRESS AND THE ADMINISTRATION OUR REQUEST FOR FUNDS AT THE NIH, MY COLLEAGUES AND I HAVE EMPHASIZED THE INTANGIBLE AND INCALCULABLE HUMAN BENEFITS--THE

IMPROVEMENTS IN THE QUALITY OF LIFE--THAT HAVE COME FROM RESEARCH. AND, FRANKLY, I CANNOT SUGGEST A BETTER REASON FOR THE CURRENT NATIONAL INVESTMENT IN BIOMEDICAL RESEARCH AND DEVELOPMENT.

BUT THERE IS ANOTHER EFFECT OF BIOMEDICAL RESEARCH--A BENEFIT THAT IS PERHAPS MORE EVIDENT TO ECONOMISTS THAN TO BIOSCIENTISTS. WE ARE NOT ACCUSTOMED TO VIEWING BIOMEDICAL RESEARCH AS A FINANCIER MIGHT SCRUTINIZE THE COST-BENEFIT TRACK RECORD OF AN INDUSTRY.

A FIVE-YEAR STUDY ATTEMPTING TO QUANTIFY THE WORTH OF BIOMEDICAL RESEARCH WAS CONDUCTED IN THE UNITED STATES IN THE LATE SEVENTIES. THE RESULTS WERE PUBLISHED IN 1979 IN A BOOK BY SELMA J. MUSHKIN TITLED, "BIOMEDICAL RESEARCH: COSTS AND BENEFITS." THE STUDY ADDRESSED THE QUESTION, "IS THE PUBLIC GETTING AN APPROPRIATE RETURN FOR THE MULTIBILLION DOLLAR YEARLY EXPENDITURE ON HEALTH RESEARCH?"

THE ANSWER WAS AN EMPHATIC "YES" WHEN THE MEASURES USED INCLUDED ACTUARIAL ESTIMATES OF THE DOLLAR VALUE OF THE PRODUCTIVITY OF THE LIVES SAVED AND THE YEARS OF SICKNESS AVERTED. FOR THE 75-YEAR PERIOD BEGINNING IN 1900, THE RATIO OF TOTAL CUMULATIVE BENEFITS TO TOTAL RESEARCH AND DEVELOPMENT COSTS WAS ABOUT 13 TO 1. IN MORE RECENT YEARS SINCE 1920, THE RATIO WAS 5 TO 1. THE RECENT SOMEWHAT LOWER BUT STILL SPECTACULAR

RETURN INCLUDES THE HIGH LEVEL OF BASIC RESEARCH DURING THE PAST 40 YEARS WHOSE PAYOFFS ARE CERTAIN TO AFFECT STRONGLY AND FAVORABLY THE FUTURE RATIOS OF BENEFITS TO COSTS.

HOWEVER, SUCH STUDIES, BECAUSE THEY ARE BASED ON THE COST-OF-ILLNESS MODEL, HAVE BEEN CRITICIZED ON ETHICAL GROUNDS. STEPHEN STRICKLAND HAS ARGUED THAT VALUING PEOPLES' LIVES IN THIS WAY "CARRIED AN UNACCEPTABLE IMPLICATION THAT PEOPLE SHOULD BE PROTECTED, OR SAVED, IN PROPORTION TO THEIR ECONOMIC PRODUCTIVITY AND PERSONAL EARNINGS."<sup>1</sup>

IN ADDITION, ALL SUCH ECONOMETRIC ANALYSES MUST BE VIEWED WITH A CERTAIN DEGREE OF CAUTION BECAUSE OF CERTAIN INHERENT DIFFICULTIES--SEPARATING THE CONTRIBUTIONS OF BASIC AND APPLIED RESEARCH, DISTINGUISHING THE SEPARATE CONTRIBUTIONS OF PUBLIC AND PRIVATE INVESTMENTS IN BIOMEDICAL RESEARCH AND DEVELOPMENT, AND ASSIGNING IMPROVEMENT IN HEALTH TO SPECIFIC INNOVATIONS.<sup>2</sup>

THIS POINTS TO THE FALLACY INHERENT IN USING DOLLARS OR LIRA OR POUNDS OR FRANCS TO MEASURE THE COST-BENEFIT RATIO OF MEDICAL RESEARCH AND INNOVATIONS. BASICALLY, THE COSTS OF RESEARCH AND THE HEALTH BENEFITS IT MAKES POSSIBLE ARE INCOMMENSURABLE.

RECENT EVENTS HAVE HIGHLIGHTED OTHER BENEFICIAL AND TANGIBLE EFFECTS OF THE NATIONAL INVESTMENT IN BIOMEDICAL RESEARCH. FOR EXAMPLE, IN THE PAST 10 YEARS OR SO, A TOTALLY NEW INDUSTRY HAS

EMERGED FROM THE UTILIZATION OF RECOMBINANT DNA, CELL FUSION, AND RELATED TECHNOLOGIES THAT WERE DEVELOPED WITH PUBLIC FUNDS. AS A GROWTH SECTOR, THE COMMERCE DEPARTMENT PREDICTS THAT THE BIOTECHNOLOGY INDUSTRY WILL JUMP FROM ITS PRESENT ECONOMIC CONTRIBUTION BY A FACTOR OF 10 IN THE 1990S TO BE WORTH APPROXIMATELY \$100 BILLION. SIMILAR AND PERHAPS EVEN MORE SPECTACULAR FINDINGS WOULD RESULT FROM ECONOMIC CASE STUDIES OF THE IMPACT OF THE VARIOUS TECHNOLOGIES FOR IMAGING. I HAVE READ A RECENT REPORT STATING THAT ALTHOUGH MRI DIAGNOSTIC SYSTEMS ARE NOT FAR PAST THE RESEARCH STAGE, THIS EQUIPMENT HAS ALREADY EMERGED AS A SIGNIFICANT AND HIGH-GROWTH COMMERCIAL ACTIVITY. WORLDWIDE SALES ARE FORECAST TO REACH OVER \$700 MILLION BY 1988.

IN THE CONTEXT OF THESE ECONOMIC BENEFITS, WE ENCOUNTER A PARADOX; NAMELY, THAT A SUBSTANTIAL NUMBER OF MEDICINE'S DISCOVERIES IN RECENT YEARS HAVE INCREASED RATHER THAN DECREASED THE COSTS OF MEDICAL CARE. THIS IS AN ASPECT OF THE ECONOMICS OF RESEARCH ABOUT WHICH THERE HAS BEEN CONSIDERABLE PUBLIC DISCUSSION OF LATE. WRITING IN THE WASHINGTON POST, STAFF WRITER SPENCER RICH SUMMARIZED THE PREDICTIONS OF A NUMBER OF EXPERTS IN HEALTH CARE AND RESEARCH AS FOLLOWS: "COSTLY MEDICAL INNOVATIONS SUCH AS HEART AND LIVER TRANSPLANTS AND EXPENSIVE FUTURISTIC DIAGNOSTIC TECHNIQUES COULD PLUNGE THE NATION INTO VAST ADDITIONAL HEALTH EXPENDITURES OVER THE NEXT GENERATION AND CONFOUND EFFORTS TO REIN IN HEALTH OUTLAYS." WHEN CONSIDERING THIS QUESTION, HOWEVER, WE MUST NOT FORGET THAT EACH OF THESE



INNOVATIONS REPRESENTS FOR THE PATIENTS INVOLVED AND THEIR FAMILIES SUPREMELY IMPORTANT PROGRESS, HOPE, AND BENEFITS THAT CANNOT BE MEASURED,

IN SPEAKING OF THE HUMANE SIDE OF THE USE OF MODERN TECHNOLOGY AND THE PRACTICE OF MEDICINE, I AM AWARE THAT THERE ARE THOSE WHO SAY WITH SOME VALIDITY THAT AS THE TECHNOLOGY AND COMPLEXITY OF MEDICINE HAVE INCREASED, MEDICAL CARE HAS BECOME MORE INSTITUTIONALIZED AND ITS DELIVERY DEPERSONALIZED. A WIDELY HELD VIEW, PARTICULARLY AMONG NONPHYSICIANS, IS THAT THE SCIENCE AND TECHNOLOGY OF MEDICINE ARE RESPONSIBLE FOR THE PERCEIVED DECLINE OF COMPASSION IN MEDICINE AS THOUGH THERE WERE SOMETHING INHERENTLY CONTRADICTORY BETWEEN SCIENCE AND HUMANITY--BETWEEN TECHNOLOGY AND COMPASSION. THERE IS, OF COURSE, NO EVIDENCE FOR SUCH A CONTRADICTION. SCIENCE AND TECHNOLOGY UNDERLIE MOST OF THE ADVANCES OF MEDICINE THAT ENABLE CONTEMPORARY PHYSICIANS TO RENDER MORE EFFECTIVE MEDICAL CARE THAN THEIR PROFESSIONAL FOREBEARS WERE ABLE TO OFFER.

FROM THIS PERSPECTIVE, COMPUTED TOMOGRAPHY, FOR EXAMPLE, CAN BE VIEWED AS A TECHNOLOGIC ADVANCE OF EXTRAORDINARY COMPASSION. AS POINTED OUT BY DR. S. M. GLICK, ITS USE HAS SPARED PATIENTS MANY DIFFICULT, PAINFUL AND DANGEROUS PROCEDURES AND HAS PERMITTED DEFINITIVE DIAGNOSIS TO BE MADE EARLIER.<sup>3</sup> WITH RECENT ADVANCES IN TOMOGRAPHY AND ULTRASOUND, EXPLORATORY SURGERY, FOR EXAMPLE, HAS BECOME ALMOST A THING OF THE PAST. GOOD SCIENCE AND

COMPLEX TECHNOLOGY APPLIED FOR THE BENEFIT OF THE PATIENT CONSTITUTES THE PRIME EXAMPLE OF HUMANE MEDICINE. PHYSICIANS ARE NOT MADE MORE COMPASSIONATE BY DOWNGRADING SCIENCE. ON THE OTHER HAND, THEIR EFFORTS CAN BE MADE INFINITELY MORE EFFECTIVE THROUGH THE APPLICATION OF THE FRUITS OF BASIC SCIENCE. THE CT SCANNER, FOR EXAMPLE, HAS ALTERED FOREVER THE PRACTICE OF NEUROLOGY AND NEUROSURGERY. AND MRI MAY SOON REPLACE IT AS THE SINGLE MOST VALUABLE TOOL FOR PRYING INTO THE ARMOR ENCASING THE BRAIN AND SPINAL CORD AND FOR DETECTING AND PINPOINTING NERVOUS SYSTEM DISORDERS.

JUST AS THE TREMENDOUS ADVANCES IN IMAGING INVOLVED MULTIPLE STAGES OF DEVELOPMENT--SO THE OPTIMAL USES OF SUCH PROMISING DEVICES MUST BE EVOLVED. A KIND OF NEWTON'S THIRD LAW OPERATES WITH RESPECT TO THE POWERFUL MEANS THAT HAVE BEEN DEVELOPED IN THE PAST FEW GENERATIONS FOR THE DIAGNOSIS, TREATMENT, OR PREVENTION OF DISEASE. THE SAME CAPABILITIES THAT MAKE SUCH MEASURES TREMENDOUSLY USEFUL CAN ALSO MAKE THEM CAPABLE OF SERIOUS ABUSE.

LET ME MENTION A FEW EXAMPLES OF WELL-INTENTIONED BUT POTENTIALLY DANGEROUS MISUSE OF MEDICAL DEVICES. MOST OF US WELL REMEMBER MASS X-RAY SCREENING FOR TUBERCULOSIS. IT WAS LESS THAN 10 YEARS AGO WHEN OUR AGENCY, THE NIH, DECIDED TO TERMINATE ITS SUPPORT FOR THE USE OF X-RAYS IN MASS SCREENING FOR BREAST CANCER WHEN QUESTIONS WERE RAISED ABOUT THE RELATIVE VALUE OF SCREENING

COMPARED TO POSSIBLE RISKS INVOLVED WITH EXPOSURE TO THE IONIZING RADIATION. NO CONCERN WAS EXPRESSED OR INTENDED REGARDING THE OBVIOUS VALUE AND IMPORTANCE OF DIAGNOSTIC X-RAY EXAMINATION OF THE BREAST IN WOMEN WITH SIGNS AND/OR SYMPTOMS WHICH MIGHT BE RELATED TO BREAST CANCER.

WHILE THE NEWER TECHNIQUES FOR IMAGING HAVE LARGELY ELIMINATED THE HAZARDOUS ASPECTS OF THE FORMER METHODS, THERE HAS BEEN SOME TENDENCY TO EMPLOY THESE COMPLEX AND EXPENSIVE DEVICES FOR LESS THAN OPTIMAL IF NOT TRIVIAL PURPOSES. AMNIOCENTESIS FOR PRENATAL SEX DETERMINATION IS AN EXAMPLE OF EMPLOYMENT OF A MEDICAL TECHNOLOGY--AND ONE WHICH CARRIES RISKS--FOR A TRIVIAL REASON. ONE MIGHT ALSO QUESTION THE ROUTINE APPLICATION OF SOPHISTICATED DIAGNOSTIC TECHNOLOGIES TO DISEASES FOR WHICH NO TREATMENT IS AVAILABLE.

FORTUNATELY, DESPITE OUR TREMENDOUS EMPHASIS IN THE UNITED STATES ON COST-CUTTING, NO ONE TO DATE HAS SUGGESTED SERIOUSLY THAT WE CURTAIL BIOMEDICAL RESEARCH--AND THE TECHNOLOGICAL ADVANCES THAT DERIVE FROM THAT RESEARCH--IN ORDER TO CONTAIN RISING HEALTH CARE EXPENDITURES. WE ARE, HOWEVER, LEFT WITH SEVERAL CHALLENGES IN THIS REGARD. FIRST, TO CONTINUE TO GAIN SUPPORT FOR RESEARCH--PARTICULARLY BASIC RESEARCH--THAT WILL BRING US BEYOND THE HIGHLY EXPENSIVE HALFWAY POINT IN TREATMENT OF DISEASES AND UP TO THE POINT WHERE WE KNOW ENOUGH TO MAKE IMPORTANT CONTRIBUTIONS TO DISEASE PREVENTION. AND SECOND, TO

DEVELOP DATA MORE USEFUL IN CONVINCING THOSE WHO MAKE DECISIONS ABOUT SPENDING FOR BIOMEDICAL RESEARCH, THAT RESEARCH--AND NEW TECHNOLOGY STEMMING FROM THAT RESEARCH--IF PROPERLY APPLIED ALSO ULTIMATELY CONTRIBUTES TO COST SAVINGS IN HEALTH CARE.

SCIENTIFIC PAPERS ON THE CLINICAL APPLICATIONS OF MRI ARE MOUNTING RAPIDLY. AND, INDEED, IT SEEMS CLEAR THAT MRI--GIVEN ITS TECHNICAL CAPABILITIES AND CLEAR SAFETY ADVANTAGES--MAY BE SUPERIOR IN MANY WAYS TO OTHER DIAGNOSTIC IMAGING. LARGE-SCALE, RIGOROUSLY DESIGNED CLINICAL RESEARCH TRIALS STUDYING MRI OR COMPARING MRI WITH OTHER MODALITIES ARE ONLY NOW BEGINNING, AND THESE ARE FEW. THE CLINICAL NICHE FOR MRI WILL BE SORTED OUT IN TIME, BUT IT WILL TAKE TIME FOR MRI TO EMERGE IN ALL ITS RICHNESS, GIVEN THE SUBTECHNOLOGIES THIS FIELD EMBRACES. FURTHER, MRI HAS NOT YET BEEN SUBMITTED TO A THOROUGH EVALUATION ACROSS A RANGE OF IMPORTANT ASPECTS: TECHNICAL CAPABILITIES, DIAGNOSTIC ACCURACY, DIAGNOSTIC IMPACT, THERAPEUTIC IMPACT AND PATIENT HEALTH OUTCOME. TO DATE, VERY FEW STUDIES HAVE BEEN PUBLISHED IN THE HOSPITAL SETTING, OF THE ECONOMIC COSTS OF THIS TECHNOLOGY.

AS MANY OF YOU KNOW, THE NATIONAL INSTITUTES OF HEALTH, THROUGH ITS OFFICE OF MEDICAL APPLICATIONS OF RESEARCH (OMAR), HAS HAD IN PLACE SINCE 1977 A MECHANISM--THE CONSENSUS DEVELOPMENT CONFERENCE--TO HELP THE MEDICAL COMMUNITY DRAW CONCLUSIONS ABOUT EMERGING OR ESTABLISHED MEDICAL TECHNOLOGIES.



BACK IN 1981 OMAR BROUGHT TOGETHER A GROUP OF RESEARCHERS, CLINICIANS, AND CONSUMER GROUPS TO EXAMINE EXISTING SCIENTIFIC EVIDENCE RELATED TO CT SCANNING OF THE BRAIN.

THE CONSENSUS PANEL CONCLUDED--EVEN THEN--THAT THE CT WAS A SAFE, ACCURATE AND POWERFUL TOOL IN THE PRIMARY DIAGNOSIS OF, AMONG OTHER CONDITIONS, BRAIN TUMORS, BRAIN HEMORRHAGES, EFFECTS OF MAJOR HEAD INJURY, AND CERTAIN INFECTIONS OF THE BRAIN. GIVEN ITS SPEED, ACCURACY AND LOW DOSAGE, THEY SAID, CT APPROPRIATELY DISPLACES A NUMBER OF OTHER RADIOLOGIC DIAGNOSTIC PROCEDURES, MANY OF WHICH IN COMPARISON ARE MORE UNCOMFORTABLE, MORE DANGEROUS, AND MORE COSTLY TO THE PATIENT.

NIH IS CURRENTLY PLANNING A SIMILAR CONSENSUS DEVELOPMENT CONFERENCE ON MRI TO BE HELD IN OCTOBER OF 1987. THAT CONFERENCE WILL INCLUDE AN EXAMINATION OF CURRENT DATA ON THE RISKS OF MRI AND ITS CLINICAL APPLICATIONS ACROSS A WIDE RANGE. IT IS DESIGNED TO ANSWER FOUR SPECIFIC QUESTIONS: ARE THERE ANY CONTRAINDICATIONS TO OR RISKS OF MRI? WHAT ARE THE TECHNOLOGICAL ADVANTAGES AND LIMITATIONS OF MRI? WHAT ARE THE CLINICAL INDICATIONS FOR MRI AND HOW DOES IT COMPARE WITH OTHER DIAGNOSTIC MODALITIES? AND, FINALLY, WHAT ARE THE DIRECTIONS FOR FUTURE RESEARCH IN MRI?

WITH REGARD TO GATHERING PRIMARY INFORMATION ABOUT IMAGING TECHNOLOGIES, THE NIH SUPPORTS AND CONDUCTS A NUMBER OF RELEVANT

RESEARCH PROJECTS. IN FISCAL YEAR 1986, NIH SUPPORTED APPROXIMATELY 300 STUDIES DIRECTLY RELATING TO MRI AND MR SPECTROSCOPY AT A LEVEL OF ABOUT \$37 MILLION. FUNDING OF THESE 300 PROJECTS COMES FROM NEARLY ALL OF NIH'S COMPONENTS, WITH THE NATIONAL CANCER INSTITUTE, THE NATIONAL HEART, LUNG, AND BLOOD INSTITUTE, THE NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES, AND THE DIVISION OF RESEARCH RESOURCES CONTRIBUTING THE LARGEST SUPPORT.

OF SPECIAL INTEREST ARE STUDIES UNDERWAY AT FIVE INSTITUTIONS SUPPORTED THROUGH THE NCI. THESE TOGETHER MAKE UP A COLLABORATIVE PROGRAM COMPARING MRI WITH OTHER IMAGING TECHNOLOGIES--FOR EXAMPLE, CT, TECHNETIUM 99M SCANNING, AND CONTRAST MYELOGRAPHY. TWO TYPES OF PATIENTS ARE BEING STUDIED--THOSE FOR WHICH THE PATHOLOGY IS NOT KNOWN AND NO IMAGING HAS BEEN PERFORMED AND THOSE IN WHICH THE PATHOLOGY IS KNOWN AND A REFINED COMPARISON OF EFFICACY IS SOUGHT. RESULTS FROM THESE NCI SUPPORTED STUDIES--ON PATIENTS WITH CNS NEOPLASMS, CERVICAL NEOPLASMS, UTERINE NEOPLASMS AND MUSCULOSKELETAL NEOPLASMS--WILL BE PARTICULARLY IMPORTANT AS MOST AVAILABLE STUDIES TO DATE HAVE NOT BEEN CONTROLLED COMPARISONS CARRIED OUT WITH BLINDED READINGS OF IMAGES AND STATISTICAL ANALYSIS OF RESULTS.

I SHOULD ALSO ADD THAT THE NIH INTRAMURAL PROGRAM IS ALSO ATTEMPTING TO ADD TO OUR KNOWLEDGE ABOUT THE ROLE OF MRI IN THE

RESEARCH AND THE CLINICAL SETTING. APPROXIMATELY 30 PROJECTS ARE UNDERWAY, INCLUDING BASIC STUDIES ON THE TECHNOLOGY ITSELF AND CLINICAL PROJECTS AIMED, FOR EXAMPLE, AT POST-TRAUMA PARAPLEGIA; CEREBELLOPONTINE ANGLE TUMORS--ACOUSTIC NEUROMAS; MULTIPLE SCLEROSIS; PEDIATRIC AND ADULT DEVELOPMENTAL DYSLEXIAS; AND IRON STORAGE OVERLOAD STUDIES IN THE HEART, PITUITARY AND PANCREAS. IN ADDITION, STUDIES WILL BE MADE OF SEPTAL ASYMMETRY AND CARDIAC OUTFLOW, AND PRESURGICAL MRI IMAGING FOR LUNG CANCER, FOR OVARIAN CARCINOMA, OR PEDIATRIC SARCOMAS OF THE EXTREMITIES.

FROM SUCH STUDIES, WE AND OTHER INSTITUTIONS HOPE TO ADD TO THE GENERAL INFORMATION ABOUT THE OPTIMAL USES OF CURRENT AND FUTURE IMAGING TECHNIQUES.

CLEARLY, DILIGENT EFFORTS IN TECHNOLOGY ASSESSMENT, FOLLOWED BY DISSEMINATION OF THE RESULTS OF THOSE ASSESSMENTS, PLUS SOUND POLICY DECISIONS ARE CRUCIAL UNDERTAKINGS. IF TECHNOLOGY IN MEDICINE MUST BE CONTROLLED, SURELY IT IS BETTER THAT IT BE MANAGED CLOSER TO THE "APPLICATION" END OF THE SPECTRUM THAN AT THE KNOWLEDGE ACQUISITION END. TO CRIPPLE BIOMEDICAL RESEARCH IN ANY WAY IN AN EFFORT TO CUT HEALTH CARE COSTS WOULD BE SHORTSIGHTED AT BEST.

IN CLOSING, PERMIT ME TO USE THE FAMILIAR QUOTATION FROM LEWIS THOMAS, IN WHICH HE ADDED "HALFWAY TECHNOLOGY" TO OUR LEXICON AND STATED A TRUTH ABOUT WHICH WE NEED TO BE REMINDED

PERIODICALLY. HERE ARE HIS WORDS: "I SAY THAT WE MUST CONTINUE DOING BIOMEDICAL RESEARCH ON ABOUT THE SAME SCALE AND SCOPE AS IN THE PAST 20 YEARS WITH EXPANSION AND GROWTH OF THE ENTERPRISE BEING DEPENDENT ON WHERE NEW LEADS SEEM TO BE TAKING US. IT IS AN EXPENSIVE UNDERTAKING....BUT IT IS STILL NOTHING LIKE AS EXPENSIVE AS TRYING TO LIVE WITH THE HALFWAY TECHNOLOGIES WE ARE OBLIGATED TO DEPEND ON IN MEDICINE TODAY: IF WE ARE TO TRY TO STAY WITH THESE FOR THE REST OF THE CENTURY, THE COST WILL GO THROUGH THE IONOSPHERE."



## REFERENCES

1. STEPHEN P. STRICKLAND, RESEARCH AND THE HEALTH OF AMERICANS  
(LEXINGTON, MA: LEXINGTON BOOKS 1978), P.45.
2. JEFFREY R. HARRIS, "BIOMEDICAL RESEARCH AND DEVELOPMENT;  
MEASURING THE RETURNS ON INVESTMENT," CURRENTLY UNPUBLISHED  
TYPESCRIPT OF THE NATIONAL ACADEMY OF SCIENCES, NOVEMBER  
1985.
3. GLICK, S.M.: HUMANISTIC MEDICINE IN A MODERN AGE, NEW  
ENGLAND JOURNAL OF MEDICINE, 304:1036, 1981.

REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

Speaking for all who are associated with the National Institutes of Health, I wish to say how deeply we appreciate this birthday gift and the warm congratulations you have extended to us. This expression on behalf of the members of the Association of American Medical Colleges has special meaning to us, for it symbolizes the relationship with academic medicine that has been a cornerstone of NIH plans and policies for 40 years.

At the century mark one is permitted to give some attention to history and to evaluate from a long range perspective the significance of things that have happened. Permit me to mention one such development that probably was the most significant event in NIH's history, namely, the emergence of extramural programs as the principal mechanisms for carrying out our mission. The fruitful partnership with academia thus created has been highly beneficial to the NIH, to medical education, and most importantly to the health of the American people.

It was the beginning of the modern NIH when the small Government laboratory, then conducting mostly in-house research, was given responsibility for administering some 250 ongoing research projects being supported during World War II at academic institutions, medical schools and hospitals.

These projects had been initiated by the Office of Scientific Research and Development that in 1945 was going out of business. The high-level decision to transfer the grants to NIH not only confirmed our role as the principal biomedical research arm of the Federal Government, it also established extramural grants as a powerful mechanism for the support of research and research training. The transfer meant that the Government intended to continue the sponsorship of research on a substantial scale.

---

\*Delivered in New Orleans, Louisiana, October 27, 1986, at the AAMC annual meeting, where Dr. Wyngaarden was presented an AAMC award in recognition of the NIH Centennial.

\*\*Director, National Institutes of Health, Bethesda, Maryland

In the intervening years the expenditures per year for grants grew from less than \$1 million in 1946 to the 1986 total of \$4 billion. The share of NIH budget dedicated to extramural research support has increased from about one-fourth in 1946 to the current ratio of almost nine-tenths. More to the point, our latest tabulation shows that in 1985, 52 percent of all extramural awards made by NIH went to American medical schools--the membership of this organization. Together we can take pride in the enormous strides that have been made in science--for the doors that have been opened to new and highly promising areas for productive research, but most of all for the improvements in health that have been realized and the ones that will come.

In planning our centennial activities we had two objectives. First, to improve the public's understanding of the worth and benefit of biomedical research and of the essential roles played by the partners in discovery--academia, the private sector, and the Federal Government. We can remind the American people of how far medicine has come in the past century. Our second objective is to attract more bright, young people into the adventure of medical research. We are beginning to realize the awesome potential of modern medicine and of modern research techniques, but we need to remind young people of how far we have yet to go.

Your gift and your strong encouragement will help us to attain our centennial objectives. Please accept our sincere thanks.

230

# MULTIDIMENSIONAL COOPERATION IN BIOMEDICAL RESEARCH\*

by

James B. Wyngaarden, M.D.\*\*

My remarks today will concern two areas of substantial interest to the scientific community. Each illustrates the range of interrelationships that is essential at the beginnings of new ventures in biomedical research as well as during the continued development of new applications of such knowledge.

As one example, I will describe some of the events involved in the emergence of the powerful technique of recombinant DNA. For the other example, I will tell of some of the discussions currently taking place with regard to the possibility of characterizing the human genome.

So much has happened in so short a time that it comes as something of a surprise to recall that it was only 12 years ago that a group of some of America's most distinguished scientists called for a voluntary deferral of research at an exciting frontier. They asked all of their scientific colleagues to join them in a "moratorium" on further studies using recombinant DNA (or gene splicing) pending an international meeting of experts to discuss potential problems. They also suggested that such research be halted to await the establishment of a committee by the National Institutes of Health charged to draft guidelines for the safe conduct of recombinant DNA experimentation, and to oversee the performance of experiments designed to assess its risks.

---

\*Address presented at the Montedison Conference on Science and Technology: Between International Cooperation and Competition, Washington, DC, November 6, 1986.

\*\*Director, National Institutes of Health, Bethesda, Maryland



The requested international meeting, under the sponsorship of the National Academy of Sciences, was held at the Asilomar Conference Center in California in February 1975. Among others attending, along with leading molecular biologists from around the world, were three lawyers and more than a dozen invited science writers.

Although there were notes of caution about overreacting to the potential hazards, most of the presentations at Asilomar related to perceived dangers. The day after the Asilomar conference, the NIH Recombinant DNA Advisory Committee (RAC) held its first meeting. The Committee was charged to ascertain whether there were certain experiments that should be prohibited, and to determine the conditions of containment, both physical and biological, which should be followed during the conduct of the permitted types of experiments. This Committee was also asked to sponsor the performance of risk assessment experiments. The RAC produced proposed Guidelines for the Conduct of Recombinant DNA Research. Based upon public hearings and extensive public comment, the proposed Guidelines were modified and finally promulgated in July 1976.

At the core of the Guidelines was the conviction that unknown hazards merited cautious handling. To minimize the chance that organisms containing recombinant DNA might escape from the laboratory, all experiments required safety barriers; those studies classed as potentially more dangerous warranted higher levels of "containment." Physical safety barriers were spelled out in detail; biological containment, a concept developed at Asilomar, called for the use of organisms that had been weakened so that they would not survive outside laboratory conditions. Certain categories of experiments were banned altogether.

The original 1976 Guidelines had been in place only a short time when it became apparent that they needed major revision. Both growing experience and scientific advances demonstrated that earlier fears about risks had been exaggerated, and that the original safety rules were unnecessarily restrictive. Moreover, new types of recombinant DNA experiments, unanticipated by the Guidelines, were being devised.

The revision process--review of proposals, public hearings, scientific meetings, and more hearings--took almost two years. The new Guidelines, issued in 1978, reflected growing assurance that earlier fears had been overstated. Subsequent revisions, put forward or proposed at least annually since 1978, continued this trend.

As recombinant DNA technology flourished, the RAC came to wield enormous influence. The NIH Guidelines originally applied only to research funded by the NIH, but other Federal agencies then adopted them, and non-Federally funded researchers in private industry voluntarily opted to submit protocols for their experiments to the RAC and to abide by its advice. The NIH Guidelines became the model for similar safety standards adopted in other countries. The system worked so well that although numerous bills to regulate recombinant DNA were introduced into U.S. Congress, none became law. By the 1980s the RAC was reviewing proposals for agricultural and industrial applications as well as biomedical research.

Some RAC recommendations have been challenged. In the 1970s a few local communities banned certain types of experiments within their jurisdictions. Recently, an NIH-approved field test was contested in the courts.

The role of the RAC is undergoing change. The Federal Government's traditional regulatory agencies have gradually evolved their own mechanisms for reviewing those applications using recombinant DNA technology that fall within their purview, and a new Federal policy governing the release of biotechnology products shifts much of the responsibility for oversight from NIH to the appropriate regulatory agencies such as FDA, EPA, and USDA. To coordinate these activities the White House, in 1985, established the Biotechnology Science Coordinating Committee, comprised of agency or department heads or their deputies. Within the new framework NIH, through the RAC, will continue to evaluate recombinant DNA experiments at grantee institutions, particularly the Nation's universities.

As would be expected, the international conference held in Asilomar in 1975 was the beginning step for a number of countries, as well as the

United States, in efforts to establish appropriate mechanisms for the nurture of research with the 'new' technologies, and at the same time to deal with concerns about unknown potential hazards.

In May of this year the "Report of a Review and Analysis of International Biotechnology Regulations" was published. This study, sponsored by a consortium of U.S. Government agencies, involved identification, review, and analysis of existing and proposed laws, regulations and guidelines pertaining to biotechnology-derived products and biotechnology processes in Japan, West Germany, France, and the European economic community.

The principal findings and conclusions underline the fact that considerable variation exists in the number and type of regulations and guidelines issued by the countries studied.

As we have done in the United States, each country studied has, or soon will have, liberalized its recombinant DNA research guidelines.

Government policy makers and regulators in all the countries surveyed rely heavily on the affected industries to supply up-to-date technical information and scientific advice.

Ethical considerations associated with human gene therapy may stimulate development of more restrictive biotechnology policies and regulations in some of the countries.

At the national level in some countries, jurisdictional and coordination issues among different government agencies are beginning to be addressed. The study concluded that if left unresolved such issues may adversely affect development of international biotechnology policies and regulations.

It would be difficult to think of a subject that fits more squarely into a discussion of international cooperation and competition than biotechnology. Certainly multidimensional cooperation has been essential to the emergence of recombinant DNA as a versatile and powerful technique.



I will turn now to the second example proposed at the beginning of my remarks as an illustration of the essentiality of varied interrelationships in the pursuit of important research activities. Molecular biology has progressed to the point now where it is now possible to characterize the human genome by obtaining complete nucleotide sequences of its three billion components.

In some ways the situation is similar to that obtaining at the time of the Asilomar conference on recombinant DNA. Now, as then, leaders in science have reacted promptly to new advances in techniques that make it reasonable to consider a giant step whose implications are profound. The current situation differs in one major way, however, from the pre-Asilomar status of recombinant DNA research. Then there was concern about proceeding because of the possibility of unknown environmental hazards. Characterizing the human genome poses no such risks but doubts have been expressed about the wisdom of committing the enormous resources that would be required for an all-out accelerated program. Dr. Donald S. Fredrickson, who was Director of NIH and took the lead in the agency's response to the recombinant DNA challenges, in comparing that event to the current situation said, "We now face a new challenge, this time more awesome than dangerous." It is in this context that international cooperation can play a tremendously important role, because the task is so huge there is no place for unnecessary duplication of efforts, and scientists throughout the world can contribute significantly to accomplishing this project.

During the past year there have been several important conferences of leading scientists who met to assess the feasibility of mapping and sequencing or deciphering and analyzing all the messages of all the genes in the human body.

In March the Department of Energy sponsored a workshop in Santa Fe attended by more than 40 scientists from the United States and Europe. Participants in the workshop were virtually unanimous in their strong advocacy of the massive biomedical and biophysical effort needed to complete this project. Perceptions of the potential benefits, although highly favorable, differed from discipline to discipline, and the enthusiasm



was high. A bit later in the year, a symposium was held at Cold Spring Harbor, New York, with the ambitious title "Molecular Biology of Homo Sapiens." At this conference there was a mixed reaction regarding the wisdom of proceeding immediately in a comprehensive project of the required scale, with the suggestion that more productive means to obtain the needed knowledge could be found short of a so-called "Big Science" project to sequence the entire human genome.

This modified approach was further endorsed at an international conference held in late July at the NIH, sponsored by the Howard Hughes Medical Institute. The sentiment of the participants in the July meeting favored making mapping of the human genetic structure the first phase of an international effort. The investment of time and effort in the second phase, sequencing, would depend on the state of technology and the proportion of the genome that is considered worth sequencing.

In mid-October the NIH Director's Advisory Committee devoted the entire agenda of its fall meeting to "The Human Genome." Participants in the meeting included scientists from academic institutions at the forefront of molecular biology and information science, as well as research leaders from the NIH, U.S. Department of Energy, the National Science Foundation, the National Academy of Sciences, the Howard Hughes Medical Institute, and the European Molecular Biology Laboratory. During the day and a half of intensive discussions of the challenge, four major topics were addressed: Why should such a massive project be considered and of what importance is the knowledge gained? Is there a realistic possibility that the project can be accomplished? What is the best way to carry out the task?; and, What will it cost?

I have mentioned that at an earlier meeting, the one in Santa Fe, the possible benefits of characterizing the human genome were seen favorably but differently by persons from different disciplines. Just to name a few of these benefits--this new knowledge would greatly enhance our understanding of the molecular mechanisms that control gene expression, and the molecular bases for inherited disease; we would gain substantial new information on neoplastic and malignant disorders as well as on autoimmune and immune

deficiency diseases; an extensive new science base would be created of special importance to studies of toxicology and the effects of environmental contaminants; and the potential for effective gene therapy would be enhanced.

It is clear that the technology exists for completing a major portion, if not all, of the task. There is general confidence that the necessary improvements in methodology will be developed to deal with certain problem areas and thus make possible the total characterization.

The most pressing problem is to devise means for dealing with the vast amount of data that will be generated by the genome project. Databases established to handle DNA sequence information are currently swamped. GenBank, which is the United States' database, was planned and launched by the NIH's National Institute of General Medical Sciences. It is funded as an interagency project, involving the Departments of Energy and Defense, and the National Science Foundation, as well as four components of the NIH. GenBank is located at the Los Alamos National Laboratory. The European Molecular Biology Laboratory (EMBL) at Heidelberg established a DNA database in 1980. Formal collaborative arrangements were established between GenBank and EMBL in 1982. It has been estimated that both of the bases have grown 25 fold in the short period that they have been in operation, and that the genome project would call for the handling and storage of 1000 times as much information as is currently being processed.

International cooperation will be essential if chaos is to be avoided in dealing with the information generated from mapping and sequencing activities taking place in many different parts of the world. Such matters as adherence to uniformity of terminology can become a final determinant of the success of the genome effort.

Given the available and prospective techniques, and information handling systems, what strategies are called for? All in all, while there seems to be no doubt about the wisdom of proceeding, it was the consensus at our recent Advisory Committee meeting that a carefully-planned stepwise effort rather than a mass attack is the method of choice. This would call

for a phased approach: first, mapping of relatively large segments of the genome; then, determining the precise sequence of bases in segments of particular interest because they are involved in genetic diseases or bodily processes. This approach would defer, at least for a time, determination of the sequences of the rest of the genome. Such an approach implies many decision points, a dynamic process that would require continuing attention from all the agencies, institutions and organizations having interest in and commitment to the project. I could envision a consortium approach--multidimensional, international in scope--involving governments, foundations, academic institutions, and industry.

If approached in accordance with this suggestion, the initial expense would be within reach. It has been estimated that to prepare a macro map of restriction fragments would require about \$100 million over a five-year period. This is well within the current NIH budget. Full sequencing will follow and will be within financial feasibility, if attention is first directed toward development of more efficient methods for cloning of gene fragments. Widespread collaboration--multidimensional cooperation--will be required at each step of this significant undertaking.

# THE QUEST FOR NEW KNOWLEDGE\*

by

JAMES B. WYNGAARDEN, M.D.\*\*

It is a very great pleasure for me to address this group this evening. In looking over the agenda for your three-day meeting, I am struck by the array of concerns encompassed by the developmental disabilities. To serve in this field, it is clear, you need a very wide range of interests and a great deal of energy to keep current with the body of knowledge connected with your work. That is one reason, I am sure, that meetings such as this one are so important. Your mission is challenging--because so many are stricken with developmental disabilities and because so much remains to be learned about how to prevent these handicapping conditions and help those already afflicted. On the other hand, it should fuel your enthusiasm to know that so many are concerned, involved, and contributing to solutions. One might say that this field, more than most, consists of compelling opportunities disguised as insoluble dilemmas.

---

\*Conference Keynote Address at American Association of University Affiliated Programs for Persons with Developmental Disabilities, Boston, Massachusetts, November 9, 1986.

\*\*Director, National Institutes of Health, Bethesda, Maryland



While your career challenges are great, my challenge for this evening is similarly so, for in order to approach the topic of "the quest for new knowledge" as it relates to the developmental disabilities, a very, very wide net must be cast. We need to look to the behavioral and the biological sciences, to basic research and clinical applications, and at developmental as well as disease-oriented efforts. All of the medical disciplines have a great deal to contribute: pediatrics, obstetrics and gynecology, psychology, neurology, genetics, molecular biology and the infectious diseases, for example. In the coming years, those concerned with the new imaging technologies will have an increasingly important role to play in the diagnosis of developmental disabilities.

In the past two decades we have made astonishing progress in preventing some developmental disabilities through provision of health services such as better prenatal care, improved fertility regulation, increased genetic counseling and newborn screening, more widespread vaccine programs, and better obstetric practices. And we have made great strides in helping those afflicted with developmental disabilities make the most of their endowments. All of these accomplishments, of course, are based--at least in large measure--on understandings gained from research. But we are still left with a heavy residue of morbidity--a baseline, I believe, that is due to gaps in our understanding of the human organism. Some may say that we should

concentrate all our energies on applying to the developmental disabilities the information that we already have in hand. But I believe that would be setting a fixed limit on the quality of care we can deliver to coming generations.

I think everyone in this room would agree that active support of the development of new knowledge, as well as the application of such knowledge, is extremely important. So, too, is an interchange of ideas among us. Those of us in research and those of us in delivery of services must move forward in concert.

Perhaps because the task is so great, the responsibility for research relating to the developmental disabilities has been accepted by nearly every NIH institute. For example, the National Institute of Allergy and Infectious Diseases has a major interest in the infectious diseases that may result in maldevelopment of the newborn. The National Institute of Dental Research supports important studies in bone formation in the fetus--primarily because of its interest in cleft palate and other facial defects. The National Eye Institute has interest in studies relating to eye conditions affecting the very young such as retinitis pigmentosa, amblyopia and strabismus. As many of you know, the National Institute of Neurological and Communicative Disorders and Stroke is a major supporter of research relevant to developmental problems, primarily in

epilepsy, cerebral palsy, and language, speech and hearing disorders. They also have a heavy commitment in basic studies of brain function and organization. The National Institute of Environmental Health Sciences has an active research program on teratogens in the environment, and the National Institute of General Medical Sciences supports a large number of relevant basic studies, primarily in genetics.

This cross-institute interest is extremely important in my view, and should be encouraged. Some may find the logic of decentralized efforts disburbing, but this approach makes good sense. In a research area so diverse, where there are so many unknowns, it is smart to cast a wide net. By supporting investigator-initiated research through these many Institutes, we have the greatest potential for encouraging talented, creative scientists to apply their expertise to important basic biomedical and behavioral problems. We can cite many examples from the past showing that the answers to fundamental questions in a given field sometimes spring from unexpected quarters.

As is well known to this organization, the National Institute of Child Health and Human Development has a special relationship to the community interested in the developmentally disabled. Since the inception of the Institute in 1962, a large complement of their research mission has centered on the study of normal human development. Even when the National Institute

on Aging was separated from the NICHD in 1974, the NICHD maintained its central interest in studying the process of change over time, from a perspective that cuts across disciplines (be it neurology, or physiology, or virology or embryology). Their view has been that a fuller understanding of an aberration in development is possible if one can grasp what went before and what should follow. According to the NICHD perspective, seeing the origins of disease and disability within the process of development itself, and searching for the point at which the deviation from normality becomes irreversible, places investigators in a unique position to discover preventive measures.

Of course, NICHD doesn't place all its emphasis on basic studies of developmental processes. You are all aware of its additional emphasis on studies--for example, some of those carried out in the mental retardation research centers--that are very near the application end of the research continuum.

I would like to digress somewhat and take just a moment to underscore another point--the importance of animal studies in our efforts against the developmental disabilities. Many biochemists concerned with human disease study animal models. They are interested in phylogeny, that is, in man's evolutionary antecedents, in the hope that if they understand why certain functions, forms, and activities were selected to prevail over



millenia, they can better understand normal human development and thus abnormality. Important contributions have been made toward understanding the human through fundamental studies of other organisms: the behavior of nonhuman primates; the digestive tract of the sea lion; or the comparative physiology of the kidney in the lungfish.

Some very important accomplishments in the developmental disabilities stem from studies of animals. For example, scientists first identified Rh factor on the red blood cells of rhesus monkeys in 1937. Since 1968, Rh immunoglobulin has been available to prevent the miscarriage, stillbirths and birth defects due to Rh incompatibility. Animal studies have provided vital knowledge helping physicians determine the critical balance of nutrients needed by very young premature babies who must receive total nutrition through intravenous feeding. Hundreds of thousands of epileptic patients owe the control of their seizures to new drugs originally screened in animals. In 1937, for example, scientists began studies in cats that led quickly to the discovery of phenytoin, now a widely prescribed anticonvulsant. Dogs played a vital role as models in the development and testing of a widely used surgically-implanted system to control hydrocephalus; physicians using this implanted shunt have saved many children from severe brain damage. There are numerous other examples.

I take the time to mention this matter and these examples because I believe it is vitally important for all of us who are concerned with prevention and amelioration of disease to step forward and help make clear to the public a few basic premises: first, that the use of animals is integral to our biomedical and behavioral research effort, second, that virtually every major achievement in medical research in the past century has depended on the use of animals, and third, that our research effort to improve human health could not be maintained or increased without continued reliance on experimentation with animals. All of us are adamant about the humane and conservative employment of animals in research, but we are engaged in an important struggle with so called "animal rights groups" who want to eliminate altogether the use of animals in research. And behavioral studies--even though often noninvasive--are not exempt from this effort. All of us must be willing to engage in this struggle. There is a critical need to develop a wider consensus among the citizenry, opinion molders, and elected officials on the scientific imperative of using animals in research. Such an effort will make a considerable difference in tomorrow's services to the disabled.

To return to NICHD's central role in the developmental disabilities...A recent emphasis of the Institute has been on the prevention of developmental problems, particularly mental retardation. NICHD played an important part in the development

of a means to screen newborns for one cause of mental retardation, congenital hypothyroidism. The story of this success sounds deceptively simple: Researchers in laboratories supported by NICHD developed supersensitive microassays for thyroxin and for thyroid-stimulating hormone. One of the investigators came up with the idea of using the microassay on the same blood spot used to screen newborns for PKU, a condition, incidentally, which is only one fourth as frequent as congenital hypothyroidism. Now, at a cost of about \$1 per patient, these babies are identified within the first four to six weeks of life, are given thyroid replacement hormone, and consequently show nearly normal function. Although the treatment requires taking a pill a day for a lifetime, approximately 1,000 cases of mental retardation are prevented each year.

Prevention of other handicapping conditions is not so readily at hand because we do not yet know enough about their causes. Recognizing that injury during labor and delivery no longer contributes to a high proportion of cerebral palsy, epilepsy, and mental retardation, the NICHD and the NINCDS last year appointed a group of experts in obstetrics, pediatrics, human genetics and development, teratology and epidemiology to identify pregnancy and birth-related events that may account for the continued incidence of neurological handicap among infants and children. Despite their exhaustive review of data, the

group, in their final report, concluded that little is certain about the prenatal and perinatal causes of cerebral palsy, mental retardation and epilepsy. In addition, a lack of knowledge about the mechanisms of brain plasticity and repair makes it impossible to ascribe specific abnormalities to any single event, or to predict the consequences of injury during development. Owing to this pervasive lack of knowledge, the group identified important areas for future research. Heading the list are recommendations for support for basic research on brain development. A better understanding of the myriad factors--cell differentiation, migration, proliferation, and synapse formation--that play a role in central nervous system development may yield therapies to modify or correct errors in these processes.

In a more directed approach to prevention, the NICHD has made studies of low birth weight and prematurity a high priority. Statistics explain why. Infants weighing less than 2,500g. at birth--and often as little as 800g to 1,500g--comprise about 7% of all births in the U.S. However, they account for two thirds of the approximately 40,000 infant deaths that occur each year as well as for a disproportionate amount of morbidity--in terms of mental retardation, cerebral palsy, seizures, learning problems, blindness and deafness. The incidence of such handicaps in very low birth weight children



(defined as less than 3½ lbs.) is more than 50 percent at school age.

The Institute's low birth weight initiative began in 1985 with the funding of two new Perinatal Emphasis Research Centers, one focusing on the physiology and pathophysiology of intrauterine growth retardation and the other on intrauterine fetal growth and metabolism. Scientists working in these two centers will explore the biological mechanisms that control fetal growth and how these processes go awry to produce intrauterine growth retardation. Over the next five years, multidisciplinary teams at each center will approach the problem of intrauterine growth retardation from different angles--studying physiological, hormonal, and nutritional influences.

Two new research networks to evaluate treatment used in prenatal and neonatal care were funded during fiscal year 1986. The two networks, one comprised of neonatal intensive care units, the other of maternal-fetal medicine units, will permit a faster, more effective system for evaluating treatments currently used to combat a variety of prenatal and newborn health problems. Investigators from each unit and from the NICHD will first identify major problems in obstetrics and neonatal care that are appropriate for clinical studies and set up research protocols. Over the next five years, the

researchers in each network will evaluate old therapies, modify existing therapies to improve their effectiveness and safety, and try new therapies in carefully controlled studies. Using this type of system, the most effective treatment can be applied quickly to ameliorate or prevent many of the health problems in pregnancy and the newborn. Once the best solution to a problem is identified, the researchers expect private physicians and hospitals to adopt the treatment quickly. Fourteen U.S. medical centers comprise the two networks.

In addition, a clinical trial investigating the relationship of vaginal infections to prematurity was initiated with the recruitment of 7,000 out of an eventual 15,000 pregnant women who will be screened for the presence of certain microorganisms which may be associated with preterm labor. Those women found to have the microorganisms will be treated to determine whether the organisms can be eliminated and whether doing so reduces low birth weight and preterm labor. In an ancillary effort, the Better Babies Project was designed and begun in Washington, D.C. to determine whether identifying low income women early in their pregnancies and linking them to medical and social services can reduce the incidence of low birth weight.

The Institute's priorities also include conducting targeted efforts in the areas of the biochemistry of labor and the

premature rupture of membranes and initiating a clinical trial to assess the value of routine obstetric ultrasound screening in detecting and managing intrauterine growth retardation. There are some other very exciting scientific areas which--in the future--could have profound impact upon the developmental disabilities.

Of course, one would be both shortsighted and ignorant of history not to make mention of the important role behavioral research has played and will continue to play in ameliorating the effects of mental retardation. The MR Centers and University-Affiliated Facilities have made major contributions, for example, in demonstrating the importance of early intervention and stimulation for children with mental retardation. Behavioral scientists have been on the forefront of developing new insights and techniques in this regard.

There are several other areas of major interest to NIH with important implications for the developmental disorders. The neurosciences are very productive at present. Ten years ago, only 6 neurotransmitters were known to exist. Now more than 100 have been identified. Their critical role in linking neurons to each other and to other tissues--that is, their ability to tell the brain and body what to do, feel, and think--is being explored with vigor and increasing success. Knowledge of neurotransmitters will have important clinical implications for

many neurological and communicative problems. For example, there is evidence associating epilepsy with changes in ion movement and imbalances in neurotransmitters. This clue has led scientists to test several new antiseizure compounds that act specifically on ionic movement and neural transmission.

Experiments are taking place to examine what once was considered impossible--a damaged brain cell regrowing or being repaired and forming new connections to carry its message. Scientists now know that neural regeneration is possible. If restitution of function ultimately becomes possible the implications for people with head and spinal cord damage, as well as hearing loss, will be enormous.

Impressive progress is being made in refining ways to improve hearing. The cochlear implant, a coin-sized receiver implanted in the ear to pick up electrical signals from a pocket-sized speech receiver worn on the body, enables the wearer to identify the presence of sound and some of its most basic characteristics. Using another approach, the deaf may be able to interpret the sound of the human voice as intelligible speech by means of computer-assisted speech processors. These devices under development electronically convert human speech into electrical signals, which then activate a cochlear implant.



Progress has also been made in genetics, for example, in the development of methods for pinpointing the chromosomal locations of genes, a process known as gene mapping. At last count, over 400 human genes had been definitively mapped, with another 400 tentatively mapped. Abnormalities of almost 200 of these genes are known to cause human disease; many are associated with developmental disabilities. Gene mapping represents a key step toward the development of better methods for diagnosing and treating these diseases, and will continue to be a priority activity of the NIH.

It is relatively easy to locate a gene whose protein product is known. Unfortunately, the primary protein defect has not been identified in many major disorders, such as cystic fibrosis, making it virtually impossible until recently to search for the gene or genes responsible for these diseases. A breakthrough came several years ago when researchers found that strands of DNA have patterns that vary between individuals. The more closely related people are, the more similar their DNA patterns will be. By comparing specific segments of DNA among a large number of people, some of whom have the disease for which the gene is sought, scientists can determine patterns that correspond to the presence of the defective gene. This approach has led to the discovery of stretches of genetic material associated with the genes responsible for Huntington's disease and cystic fibrosis. These so-called "markers" may form the

basis of diagnostic screening tests to determining either the absence of a particular gene or the presence of an abnormal gene.

Once markers for disease-causing genes are found and the location of these genes is pinpointed to a particular chromosome (and often, to a specific area of the chromosome), scientists can search for these genes more efficiently.

Significant advances have been made on other important fronts as well, with researchers learning more and more, for example, about the molecular machinery that works to turn genes on and off at just the right moments, and about the nature of the consequences when such machinery goes awry. Scientists are hopeful that they can eventually use the information obtained from such studies to gain an understanding of how the functioning of all genes is regulated. It is believed that this, in turn, will facilitate efforts to control some of the effects of genetic disorders.

Other scientists are working on studies that eventually may make direct gene therapy possible as a cure for genetic disorders. The long-term goal is to be able to replace a defective gene with a normal one in some or all of the body's cells. Such treatment would affect only the patient, not his or her offspring. It is currently very difficult, however, to

insert a normal gene into the correct site on a chromosome and have it be expressed in the proper amount at the proper time.

In many laboratories, great strides are being made toward the goal of effective gene therapy. Recently, scientists successfully inserted a gene into a predetermined site on a human chromosome. Working with cells grown in test tubes, these researchers managed to insert the gene for beta-globin, a component of hemoglobin, the oxygen-carrying protein of red blood cells. This gene is defective in sickle-cell anemia, as well as in a different type of anemia called thalassemia.

The work by these scientists is still in its early stages and cannot yet be applied to treat diseases. Nevertheless, it is very encouraging, because until now no one had been able to make planned modifications, such as targeted insertions, of specific genes of any organism more complicated than yeast. Their success raises the hope that modification of the defective beta-globin gene will be feasible as a treatment of--and perhaps ultimately a cure for--patients with genetic disorders such as thalassemia and sickle-cell anemia.

As I mentioned earlier in my talk, it is extremely important that the results of research make their way, when appropriate, into the health care setting. The NIH mission, therefore, includes responsibilities beyond knowledge

acquisition; one of these responsibilities is the transfer of knowledge.

One of the most effective means in science for interchange of information and transfer of knowledge is conferences and meetings. As many of you know, the NIH has evolved, since 1977, a mechanism--the consensus development conference--designed to help the medical community draw conclusions about emerging or established medical practices or technologies. A number of these over the years have been related directly to the developmental disabilities. For example, past conferences have dealt with antenatal diagnosis, febrile seizures and epilepsy, cesarean childbirth, defined diets for childhood hyperactivity, and diagnostic ultrasound imaging in pregnancy. These, we believe, have had impact on guiding the practice of medicine in this country.

Another major coordinating effort relating to the developmental disabilities is the Interagency Committee on Learning Disabilities, which I chair. This committee, established just about one year ago, brings together representatives of a large number of agencies in the Federal government--including the Environmental Protection Agency, Department of Energy, Centers for Disease Control, and Food and Drug Administration--with some involvement with the learning



disabilities, As some of you may know, this committee is to provide to the Congress by May of 1987 recommendations for legislation and administrative actions to increase the effectiveness of research on learning disabilities and to improve the dissemination of the findings of such research.

This group will be especially interested in a meeting scheduled for November 17-18 at the NIH sponsored jointly by the NICHD and the Joseph P. Kennedy, Jr. Foundation, "Mental Retardation: Research Accomplishments and New Frontiers". The meeting, which will mark the 25th anniversary of the founding of the NICHD and the 40th anniversary of the founding of the Kennedy Foundation takes place during the Centennial Year of the NIH, and will feature as speakers some of the most outstanding leaders in fields relating to mental retardation, including many of you in this audience. This conference will provide an opportunity to recognize advances and challenges in mental retardation research and services, as well as to honor the leaders who provided the momentum behind the establishment of the network of centers aimed at furthering understanding, treatment, and prevention of mental retardation.

I could not end my remarks this evening without making special mention of the unique role of the mental retardation research centers in connection with technology transfer activities. Because the MR centers and University-Affiliated

Facilities embrace three missions: conduct of research, patient care, and clinical training of professionals involved in treating the developmentally disabled, they hold a pivotal position in the transfer of new knowledge into application. These centers are national resources with potential not yet realized. Last year at this meeting, Dr. Duane Alexander, NICHD Director, laid out some very exciting recommendations-- collaborative clinical trials, increased interaction among centers and UAFs, and more support for the training of clinical investigators in the field. As the NICHD and the rest of the developmental disabilities community move toward these goals, I am sure we will accomplish what we all desire: a reinvigoration of the Centers for their next decades dedicated to research, training, and service.



## NURTURING THE NIH-INDUSTRIAL LINKAGE\*

by

James F. Wyngaarden, M.D.\*\*

In mid-October the National Institutes of Health began a year-long observance of its centennial, marking the 100th anniversary of its establishment in New York in 1887. We selected as a descriptive slogan "A Century of Science for Health." Just as appropriately we could have adopted the theme you have assigned to this opening session, for the history of NIH is indeed the history of "Research of and for Human Needs." Good health is a basic human need, and the mission of the NIH is to conduct and support research for new knowledge that will lead to improvement of health.

Today I will take this opportunity to tell you briefly about the National Institutes of Health and about the mechanisms it employs for the conduct and support of biomedical research. I will also describe some of the existing and developing linkages between our programs and the research endeavors of industry. A bit of history provides context for my discussion.

In the course of the past century the fund of knowledge in the biological sciences has grown at an astounding rate, particularly in recent decades, and the new knowledge has been translated into application at an accelerating pace. In the past ten years, for example, we have seen the emergence of molecular biology from the laboratory to become the basis of a variety of rapidly growing industries.

As would be expected, the National Institutes of Health has undergone organizational changes during the past century, some approaching transformations. For the first half of its history the agency was, in essence, a

---

\*Address presented at the 1987 fall meeting of the Industrial Research Institute, Boston, Massachusetts, November 10, 1986.

\*\*Director, National Institutes of Health, Bethesda, Maryland



small Federal laboratory carrying out within its own confines important research projects, but its resources were such that at any given time only a limited number of studies could be conducted. It was during the adjustment period following World War II that the transformation took place. With demobilization the Office of Scientific Research and Development (OSRD) went out of business on December 31, 1945, and some 250 biomedical research projects funded by the OSRD at universities, hospitals and other research institutions were transferred to the NIH for administration. It is significant that the research projects were not cancelled, and that instead a mechanism was put in place for continuing to award such grants and contracts. Peacetime reliance on non-Federal laboratories for the conduct of federally-supported research represented a sea change in Federal science policy and has been responsible for the establishment of the modern NIH.

By far, the largest part of NIH research takes place in nearly 1300 non-Federal laboratories, most of them within the United States, where more than \$4 billion is being expended annually from the NIH budget for biomedical research and research training. Almost 90 percent of the NIH budget is devoted to such awards and the necessary administrative costs entailed.

In addition to the grant and contract-supported extramural research, more than 2,500 government scientists participate in research at our main campus in Bethesda, at the National Institute of Environmental Health Sciences at the Research Triangle in North Carolina, at the Rocky Mountain Laboratory in Montana, and in a few small NIH installations elsewhere. These intramural scientists, their collaborating guest workers, and the laboratories where they perform their research constitute what is probably the largest resource of its kind. As large as it is, however, it is through our extramural programs that we mobilize the energies of some 50,000 American scientists who carry out research under NIH-awarded grants and contracts.

The key mechanism used by NIH for deployment of the scientific community's creative energies in biomedical research is the investigator-initiated project grant. It is used for supporting the majority of our

extramural research. Well over half or more than 55 percent of our total current budget of \$6.2 billion is allocated to the support of project grants for the conduct of research by non-Federal principal investigators. Such investigator-initiated research draws upon the expertise and intuition of practically the entire American scientific community. In recent years the number and quality of research proposals has increased steadily, so that even though our appropriations have increased from year to year we are able currently to fund only just over a third of the meritorious grant applications we receive each year.

With the rapid expansion of support for the extramural program, the number of applications for support grew even more rapidly. It was necessary to devise and develop a program for selection of the most meritorious projects by review of grant applications and contract proposals. The system used by the NIH for this critically important function has served well the interests of science and our health-related mission. The NIH peer review system has been emulated in a number of other countries. The first levels of review are performed by scientific review groups, established generally along lines of scientific disciplines or disease areas. Members of these groups are primarily non-Federal scientists selected for their training, experience and expertise in the pertinent scientific field. Such members are appointed for four-year terms.

In order to evaluate the very broad range of disciplines represented in the 20,000 or more research proposals submitted to the NIH each year, there are more than 100 initial review groups. Most of these review groups are oriented to different specific areas of science spread across the spectrum, from the study sections concerned with basic research at the molecular level to panels such as the Biotechnology Resources Review Committee or the Committee for Evaluating Developmental Therapeutics contracts.

All of the regular review groups normally meet three times each year to conduct rigorous assessment of the scientific merit of the individual proposals assigned to them. On the basis of such review, priority ratings

are given to the proposals based on their perceived scientific merit. These priority ratings are used by a second review body, the funding unit's National Advisory Council, in deciding whether or not to fund the candidate proposal. By law, each of the 12 constituent institutes of the NIH, as well as the Division of Research Resources and the National Library of Medicine, must have the approval of its Advisory Council or Board before grant awards can be made for the support of research. This second step in the dual review process provides for special emphasis in instances where the need for research in a particular field as well as the technical merit of the proposal under consideration must be considered. Recently, for example, special consideration was given to meritorious proposals related to research on AIDS.

Research grants are usually made for the periods of three years and may be renewed. Applications for renewal, however, compete with new proposals. Because of the multi-year character of research grants, the number of new or competing renewal grants that can be made in a given year depend not only upon the funds currently available, but also upon the number of grants awarded in the previous years that constitute continuing commitments. As a result there have been times when the number of new and competing renewal awards varied markedly from year to year. Because this variation had an unsettling effect upon prospective investigators, particularly young scientists at the very time they were making career choices, the Administration, the Congress, and the NIH have made a special point of attempting to assure a reasonably predictable number of new and competing renewal grants each year. The NIH appropriation for 1987, which provided an increase in funding for all NIH programs, also prescribed that we must make at least 6,200 new and competing renewal grants. These, added to our continuing commitments will bring the total number of projects to be supported by grants during the year to more than 19,600.

Our 1987 budget for project grants is \$3.45 billion; for extramural research supported by other types of grants almost \$900 million; for research supported by contracts almost exactly half a billion; for intramural research in our own laboratories about \$650 million; and for research training grants about \$230 million.



The 1987 budget for the NIH was increased overall about 17 percent over the FY 1986 budget. We recognize that an increase of this magnitude during a time of budget restraint is an indication of the level of confidence that exists in this country as to the long-term value of biomedical research. As in previous years, it results from an appreciation for the overarching importance of research that may lead to the development of new means for the prevention, treatment or cure of disease and disability. But recently the Administration and the Congress have also become interested in the direct economic consequences of the national investment that has been responsible for the emergence of biotechnology.

In this context permit me to turn to the theme of the linkages between biomedical research and industry. Biotechnology is not a phenomenon of the 1980's--in fact, it has a long history, certainly as long as the NIH. In 1887 American medical and biological science was heavily dependent upon the laboratories and research of the European giants--Pasteur, and Koch. The first director of the laboratory that later became NIH studied with Koch and spent time in Pasteur's laboratory. We sometimes forget the strong linkages between the work of Pasteur and industry. In this connection permit me to read the Encyclopedia Britannica's summation of his work: "Pasteur proved that microorganisms cause fermentation and disease; he originated and was the first to use vaccines for rabies, anthrax, and chicken cholera; he saved the wine, beer and silk industries of France and elsewhere; he performed important pioneer work in stereochemistry; he originated pasteurization." A modern version of this catalogue of accomplishments is provided by the explosive growth of processes, products and techniques that has resulted from recent basic research in molecular biology.

The new linkages that have been established between the NIH and industry have been forged during a period in which industry has supplied an increasing share of the national funding for health research and development. Twenty years ago industry as a whole was the source of funding for 24 percent of health research and development; in 1970 it had risen to 28 percent and this increased gradually until 1980 when it was 31 percent, and by 1985 industry's share had increased to 39 percent. As a footnote I



should mention that in the era of the modern NIH its contribution to national health research and development each year exceeded the total invested by industry until 1983. In 1985 NIH's share was 37 percent as compared with industry's 39.

Recent years have seen the establishment of a number of new ties between industrial organizations and some of the Nation's leading academic institutions. As I have come to know more about individual examples of such collaboration, I have been interested to note the many ingenious contractual arrangements that have been devised to serve optimally the purposes of the partners while protecting their interests with respect to freedom of inquiry, open scientific communications, and proprietary rights. The NIH has an obvious interest in such new partnerships with academic institutions that for years have been closely linked with our extramural programs. We have not interposed ourselves in the new arrangements and have no intention of doing so.

Important links between the NIH and industry were established more than 30 ago years with the establishment of the NIH patent policy in 1953. It was recognized that if important fruits of research were to be put into widespread use, substantial outlays would be needed for development and marketing. The government is not a feasible or appropriate source for most such support, but it was clear that some incentive must be offered to companies to invest in the final stages of development. It was not a simple problem. The new products and processes arising from research conducted with public funds could have been placed in the public domain. To do so, however, would have denied potential developers and marketers the kind of exclusivity that would have induced them to make the necessary additional investment. The NIH recognized that in most cases it would not be reasonable to expect a pharmaceutical company or any other industrial organization to expend funds for development of a product that would not be protected from competition.

Furthermore, the NIH could not be expected to expend funds needed for research in bringing the products of research to the American people. That

would have drained the funds required for continuation of research on many fronts.

The NIH patent policy was adopted as a means for breaking through the impasse. In the extramural programs each grantee institution was given the opportunity to enter an institutional patent agreement. Under the agreement the institutions were encouraged to patent innovations resulting from NIH-supported research and to arrange for the licensing for development and marketing of such innovations. Under the patent agreements the institutions themselves receive a major share of the royalties from such licenses but they must invest such proceeds in further biomedical research. The inventors also receive stated shares. The NIH does not participate in the income from such extramural licensing agreements.

In summary, the NIH patent program provides for promoting the transfer and commercialization of federally-funded inventions by the private sector. Inventions that result from in-house research are reported, evaluated, and submitted for patenting with the assistance of the Office of the General Counsel of the Department of Health and Human Services, the funding NIH bureau, institute or division, and the inventor.

The NIH Office of Medical Applications of Research coordinates evaluation of the invention's potential for commercial use. Experts in the major NIH components evaluate the feasibility of the invention's operational use, its novelty and scientific importance, and its potential marketability. Based on such recommendations, decision is made whether or not to proceed to apply for a patent.

Between 1980 and 1984, 282 invention reports were filed by NIH employees, for example, and of these 73 percent have been patented and 51 percent have been licensed to the private sector. In recent years, an average of 500 inventions have arisen directly from NIH-funded research, leading to the filing of an average of 210 patent applications each year.

Many of the features of the long-standing NIH patent policy were embodied in the Stevenson-Wydler Technology Innovation Act of 1980.

Amendments to the Act signed into law October 20, 1986, direct that the Federal laboratory where the invention took place receive the royalties arising from its licensing, and specify that the Federal employee who is the inventor receive not less than 15 percent of the royalties.

I will turn now to other linkages.

During the first two decades following World War II, the NIH accepted grant applications from institutions and organizations regardless of their "for-profit" or "non-profit" status. However, in the mid-60's congressional concerns prompted a change in that policy and only not-for-profit organizations were considered to be eligible for grants. This restrictive policy was abandoned in December 1982 so that applications may be received, reviewed, and if of sufficient merit awarded to industrial organizations as well as to the traditional grantees. Thus, NIH-funded programs can have access to the creative abilities of the many outstanding scientists employed by industry, and conversely these scientists have access to sources of funding for research projects that might not be appropriate objects of company support. Such grants do not now constitute more than a small fraction of our total portfolio and probably will not increase markedly in the foreseeable future. However, a new type of grant was created by the Congress in 1982 through legislation mandating that a specified percentage of the funds of Federal research agencies be awarded for research by small business organizations. The NIH Small Business Innovation Research Program funded 445 grants in 1986 for a total of \$44.5 million. Such awards are made in stages on the basis of the merit evaluations by initial review groups operating in much the same manner at the traditional research study sections assess proposals.

Before the recent policy alterations with regard to grants were made, another linkage with industry had been strengthened. Prior to the late 1970's, agency policy had not permitted appointment of industry's scientists to our initial review groups, or other scientific advisory bodies. It was perceived that such a policy prevented us from utilizing in our review process the substantial and sometimes rare abilities of scientists employed by for-profit organizations. This policy has now been changed.



In a similar way provisions have been made for mutually beneficial collaboration through guest worker appointments within the NIH intramural research program. Under this arrangement scientists from industry may come to NIH and work side by side with NIH investigators in our on-campus laboratories. The guest workers are not paid, but laboratory space and support are provided. Recent legislation covering "volunteer" workers gives a broad statutory base for such programs.

In a reciprocal arrangement, NIH scientists are now permitted to engage in so-called "outside activities," such as lecturing at or consulting with industrial organizations and receiving honoraria for doing so. For obvious reasons certain restraints must apply to government employees, and in the case of consultations prior approvals must be secured. These steps will be recognized by those of you who have been following this matter as real progress in strengthening relationships between industry and the NIH for the benefit of the American people.

Thus, at different levels there have been increasing interactions--provisions have been made to permit NIH scientists to lecture at and consult with industry, guest investigators from industry may now be accommodated within the NIH's intramural laboratories, and active collaboration between industry and NIH is taking place in a number of ways, including conferences for the direct exchange of scientific information. Two such IRI conferences have taken place at the NIH--the most recent one less than three weeks ago. In the first such exchange last year, most of the presentations were made by our intramural scientists, in the more recent conference scientists from industry made most of the presentations.

In closing I will turn to a matter in which we are linked by common concerns. The biomedical research community is being threatened by a small but determined segment of society that is opposed to the use of laboratory animals. Physicians and scientists at leading institutions, as well as in industry, are coming under increasing pressure from "animal rights groups" to eliminate or severely curtail the use of animals in research.



Antivivisectionism as a cause has flourished and ebbed in this country for more than a century. One difference between antivivisectionists and current activists is that the animal rights groups seem to be better organized and better financed, and are directed by articulate leaders, including a few philosophers, former researchers, entertainers and attorneys. While these groups engage in a spectrum of activities, many of their activities are targeted at biomedical research. Some of these groups espouse causes to which we can and in fact do subscribe: appropriate care of research animals; avoidance of unnecessary pain; use of minimal numbers of animals; use of most appropriate species; avoidance of unnecessary duplication of research; and use of model systems instead of intact animals where possible. But all too often these principled goals are coupled with a desire on the part of activist groups to eliminate completely the use of animals in research--a goal that is impossible unless we are willing to settle for today's level of health care and the indefinite persistence of human suffering and premature death.

The NIH has been the target of a sit-in and prolonged picketing, and there have been break-ins at about a score of sites in different parts of the Nation where animal research is being conducted--the most recent in laboratories in Oregon in October. There can be no justification for the theft of research animals and records, as well as the destruction of equipment. Such disruptions in research are costly in terms of time, money, and animal lives. Additional animals are required to accomplish the objectives of many of the disrupted projects.

Well coordinated attempts are underway in various states to enact laws to abolish the practice by pounds of releasing unclaimed animals for research and education. Some investigators believe this type of law is the first step toward a total ban on animal experimentation. Last year, bills were introduced in 21 state legislatures restricting the use of animals in research and testing. The majority would have prohibited the use of pound animals. During 1986 a law was enacted in Maryland precluding the use of pound animals in biomedical research.

I believe that those concerned with improving the standards of health, particularly scientists and research administrators, cannot afford to sit idly on the sidelines when actions could make a difference.

There is a critical need to develop a wider consensus among the citizenry, opinion molders--including the mass media--and elected officials on the scientific imperative of using animals in research. I believe that the current attacks on medical science must be taken seriously and that we must respond. Whether fueled by ignorance or naivete, cries to outlaw animal experimentation must be countered with scientific fact and reaffirmation of our commitment to improving human health through responsible use of animals. This truly is the humane course.

I appreciate the opportunity you have given me to meet with you and to discuss our programs and the matters in which we have many common interests. It seems inevitable that our areas of collaboration will expand and to our mutual benefit as we intensify our "research of and for human needs."



25

**The Evolution of Science at the  
National Institutes of Health and the  
National Institutes of Environmental Health Sciences\***

by

James B. Wyngaarden, M.D.\*\*

Good morning, ladies and gentlemen. I am very pleased to be with you here today at the National Institute of Environmental Health Sciences (NIEHS) to help celebrate your 20th Anniversary. I congratulate you on two decades of progress and growth as a center of scientific inquiry.

Today, and over the next two days, we will be hearing both scientific and historical presentations. We will be provided with a look at some of the most recent fruits of inquiry in the fields of fundamental biomedical research and environmental health sciences. And on Friday morning we will hear several speakers discuss the history of NIEHS and its role in the community. I am looking forward to those presentations.

As you know, the period from October of this year to October next is also an Anniversary for the National Institutes of Health itself--our 100th year. In comparison with your 20th Anniversary, for which you can bring together many of your Founding Fathers into this auditorium, NIH's 100th Anniversary makes it an old man among institutions. And with age has come wisdom, I hope.

NIH had its beginnings in a humble one-room Hygienic Laboratory on Staten Island 100 years ago. That laboratory was equipped with a modern Zeiss light microscope imported from Germany. The laboratory's primary function was to inspect cargo and persons coming into the United States from abroad for contagious disease.

In 1912, Congress changed the name of the organization which ran the laboratory from the Public Health and Marine Hospital Service to the Public Health Service (PHS). The change expanded the PHS role to include the diseases of man, pollution of navigable streams, sanitation, and sewage. Before there was an EPA and an NIEHS, pollution issues were handled by a variety of PHS entities. In June 1958 the Bayne-Jones Report recommended to Congress the establishment of an agency specifically oriented toward the conduct of biomedical research into the effects of environmental agents on human health.

---

\* Presented at the Scientific Seminar, "The Environment and Human Health: Achievements and New Directions," Research Triangle Park, NC, December 3, 1986.

\*\* Director, National Institutes of Health, Bethesda, Maryland.



After that, a coalition of social forces moved irrevocably toward the creation of a national research center devoted to studying the effects of environmental hazards on human health. These forces included: increased public awareness of air and water pollution, the disastrous effects of thalidomide in Europe, and the destruction of bird and aquatic life by pesticides; the inevitable Congressional desire to do something about the pollution problem; and the eagerness of the academic community to get into and explore a new and exciting, socially desirable field of research.

In November 1961 Dr. Paul Gross, Professor of Chemistry at Duke University, issued a similar call for creation of an institutional focus for environmental health research. The call was then taken up by a Study Group of the PHS which recommended an increased public role in environmental health research, a central laboratory. By 1962, the National Academy of Sciences/National Research Council endorsed the idea, extending the concept even further to include the university involvement. This is today a reality in the form of your 15 Environmental Health Centers at universities. A short time later, in 1966, the Surgeon General created the Division of Environmental Health Sciences and three years after that the Secretary of Health, Education and Welfare Wilbur Cohen made the Division an Institute.

Once planted in the firmament, NIEHS grew. From a handful of employees back then, NIEHS has grown to a staff of 700. And, starting from a few temporary buildings on the North Campus, you now occupy this magnificent building with its state-of-art laboratories. This steady growth is a measure of the importance which society accords your role.

NIEHS holds two distinctions among the 12 NIH Institutes. The location of your facility here in North Carolina rather than in Bethesda is a story that I suspect will be told Friday. You will have to wait for that, but a second distinction of NIEHS is its non-categorical nature. Unlike most NIH Institutes, NIEHS is not limited to examining a specific disease or organ system. Instead, NIEHS has a very broad mandate.

Your mission is to define the scientific parameters of questions concerning the mechanisms by which agents such as chemicals, light, or noise cause cancer; reproductive, neurological, or immunological effects; or genetic damage. This mission includes questions about dose-response relationships, variations from species to species, extrapolations from high to low doses, the effects of mixture and of low level exposures to agents, host defense and variations, biological markers . . . the list of appropriate areas of investigation is quite lengthy.

Within this century, man's ability to explore fundamental biological mechanisms has been enormously enhanced by amazing advances in technology such as electron microscopes, CT scanners, and Magnetic Resonance Imagers. They represent a quantum leap from the light microscopes that biologists had been using for the past 300 years. New tools and techniques have led to a scientific revolution, one which permits us to address fundamental questions about the nature of living organisms.

There has been a coalescence in language and in the techniques and methodologies of biochemistry, genetics, virology, microbiology, physiology, and even anatomy. The once inviolable lines between the disciplines have been blurred. The common language is that of molecular biology of cell structure and function.

We may no longer know what to call these new scientists--molecular geneticists, molecular biologists, biochemists, or virologists--but it is clear that there is ample scientific opportunity for them to expand their spheres of interest. The era of science heralded by the discoveries in genetics in the 1950s and the 1960s provides the broad field of biology with a set of unifying principles and properties that can be tested in almost infinite variety.

NIEHS, like other NIH Institutes, is experiencing this cross-fertilization of scientific disciplines. Your scientists are involved in collaboration with those in other disciplines and at other institutions. Your ongoing work with DNA adducts as biomarkers for assessing risk and with oncogene activation as a method of classifying carcinogens as genotoxic or promoting agents are two good examples of this process of mutual enrichment.

Although some scientific discoveries may result from serendipity, most are the product of years of teamwork that often includes researchers working together at several institutions. These teams also include graduate students and postdoctoral fellows. Such a collaboration of experienced scientists and relative newcomers is a kind of human cement that provides the historical continuity necessary to scientific progress.

I think this convocation of such impressive scientific minds from both within NIEHS and from other NIH Institutes and academia is an excellent way to begin your three-day Anniversary celebration. I look forward to hearing from our speakers.

Thank you.



# THE GENESIS OF THE NATIONAL INSTITUTES OF HEALTH\*

by

James B. Wyngaarden, M.D.\*\*

I am very pleased to be here today to celebrate the 20th anniversary of the National Institute of Environmental Health Sciences (NIEHS). Anniversaries are important because they encourage us to reflect upon where we have been and where we are going. As you know, the period from October 1986 until October 1987 is also a very important anniversary for the National Institutes of Health (NIH)--our Centennial. Both anniversaries, those of NIEHS and NIH, can be viewed fruitfully from an historical perspective.

As the NIH anniversary got closer and closer, I began to think of NIH as sort of an old man among institutions, that is, until I was invited to help celebrate an anniversary at the University of Heidelberg, its 600th. When Heidelberg--not the oldest university in Europe either, Bologna is 900 years old--opened its doors to the first student body, the New World was still waiting for Columbus to arrive. And it would have to wait almost another century.

From this humbling, more global perspective, NIH is a young institution. And compared with NIH, the NIEHS is so young that you are still able to bring many of your Founding Fathers together for this joyous anniversary celebration. And, not only are they both young institutions, both also have experienced enormous growth since their foundation.

When the NIH was founded, Europe dominated science. One hundred years ago, the standard of excellence in medical science was found in the laboratories of Koch in Germany and Pasteur in France. American scientists were excited by the new discoveries in bacteriology but they were not

---

\*Address presented at the 20th anniversary ceremony of the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, December 5, 1986.

\*\*Director, National Institutes of Health, Bethesda, Maryland



really a part of them. And, despite the fact that this country was ravaged by epidemics of yellow fever, cholera, and tuberculosis (thought to be brought in by new arrivals from Europe), medical practitioners here were painfully aware of how backward this country was medically. Efforts were made to contain the contagion at the borders, but were largely ineffective.

The NIH traces its origin to a tiny, one-room laboratory on Staten Island. It was established by the Marine Hospital Service and was called the National Hygienic Laboratory. Its European origins were frankly acknowledged in an 1887 Report by the Surgeon General to Congress. Quote: "In August, 1887, a bacteriological laboratory was established in the Port of New York....The apparatus supplied was modeled after those used in the laboratory of Dr. Koch, of the Imperial German Health Board, and is supplied with the Zeiss' latest improved microscopic objectives and microphotographic apparatus."<sup>1</sup>

The laboratory's first Director, Dr. Joseph Kinyoun, was inspired by European science and soon announced his goal. He wrote: "The Laboratory, situated and equipped as it is, should form the nucleus of one national laboratory in its character, and developed on the same lines as those in Germany, France and England."<sup>2</sup> In 1891 the laboratory moved to Washington, D.C. This move underscored the status of the laboratory as a National resource.

At first, the facility was located in the Butler Building near the Capitol, but in 1904 it was moved into newly constructed buildings that were designed for research activities. The laboratory at 25th and E Streets was the Institution's home for nearly 35 years. It was the site of many heroic and successful battles against disease.

Among the scientists associated with the Hygienic Laboratory were some of medicine's heroes. For example, Dr. Howard Taylor Ricketts, whose work on Rocky Mountain spotted fever provided the key for finding the cause of one of the great plagues of mankind--epidemic typhus. Ricketts died of typhus in 1910, a victim of the organism that he had earlier described and that subsequently was named for him--the Rickettsia.

Two years later, in 1912, Dr. T. B. McClintock was sent from the Hygienic Laboratory to Montana to carry out a project that had been planned by Dr. Ricketts. He completed the project, but in the process contracted spotted fever and died shortly after returning to Washington. Another medical hero.

The Hygienic Laboratory had one of its most dramatic and deadly crises in 1919 when an outbreak of psittacosis, often called parrot fever, occurred simultaneously in three continents, Europe, North America, and South America. Even scientists scarcely knew there was such a disease as psittacosis. It seemed to have been spread by a shipment of diseased parrots in the Christmas trade from a South American port.

Suspect parrots were brought into the Hygienic Laboratory from nearby cities and from as far away as Maine and Ohio. Within three days after the birds were brought into one of the basement laboratories, Henry Anderson, the assistant to the laboratory chief, was hospitalized and within a few days he died of psittacosis. There were at least six more deaths from the disease and several of the leading scientists in the laboratory had been seriously ill.

A giant among the remarkable members of the staff was Dr. Joseph Goldberger. Considered to be one of the most promising of the young men connected with the Hygienic Laboratory, he was placed in charge of the Public Health Service investigation of pellagra, then prevalent in the poverty-stricken South, but known as a problem in 40 states as well as the District of Columbia.

The Public Health Service was determined to make an attack on pellagra. The disease was then thought by most medical scientists to be caused by a particular organism. Dr. Goldberger argued that if a bacillus were the cause, some of the doctors and nurses and other attendants working around the pellagra patients daily would get it. He pointed out that the one difference between the inmates in prisons and mental institutions, and the people who cared for them, was their diet. Many of the inmates suffered from pellagra, whereas their attendants did not.

Dr. Goldberger's confirmatory investigation was a classic of epidemiology. A master of both observation and experimentation, Goldberger showed that the poor, monotonous diets common to many low-income people--diets high in carbohydrate and low in protein sources and fresh vegetables--induced pellagra when fed to volunteer convicts in a Mississippi penitentiary. In other public institutions where the disease occurred, investigators demonstrated that generous amounts of milk, eggs, meat, beans, and peas prevented it. Still, physicians who were treating pellagra at the time strongly believed that it was due to an infectious organism and would not accept Goldberger's evidence.

As a final proof that no infectious mechanism was involved, Goldberger and one of his collaborators injected each other with blood from a pellagra patient. Later Goldberger and four associates swallowed capsules containing patients' wastes and skin scrapings, and Goldberger injected blood from a pellagrous woman into his wife, Mary. None contracted the disease, although it is not recorded what adverse symptoms may have resulted from these heroic experiments.

He later developed a treatment using yeast in the diet and showed that the amino acid tryptophan was crucially related to the cause of the disease. Soon the B vitamin nicotinic acid, or niacin, was identified as a specific pellagra preventive.

The Ransdell Act of 1930 was a landmark in our history. It changed the name of the Hygienic Laboratory to the National Institute of Health, expanding its emphasis from concentration on infectious diseases to the broader mission of "ascertaining the cause, prevention and cure of disease." Among the events having a substantial impact on the future of NIH was the gift shortly thereafter of a large tract of land by Mr. and Mrs. Luke Wilson. In 1938, NIH moved from Foggy Bottom to its present campus which soon included six buildings. Then, a year later, war began in Europe. (Insert FDR slides and tape.)

The ascendancy of the modern NIH to its present position of world leadership in biomedical science can be traced to the changes brought by

World War II, to the uprooting of European culture and the cooperative relationships forged out of wartime necessity between the American Government and academia.

To meet the urgent health needs of the armed services, the Government turned to the established non-Federal laboratories for help in conducting vital research. Grants and contracts were awarded for the support of such essential investigations. This arrangement worked exceedingly well. These newly formed partnerships greatly accelerated progress in research and development across the spectrum, from the most basic research to studies on the widespread application of newly formulated measures for prevention, diagnosis, and treatment of disease.

By the end of the war the U.S. Office of Scientific Research and Development (OSRD) was administering a large number of medically related research projects. A leading American scientist, Dr. Vannevar Bush, the President's science advisor, urged that the Government continue to support the medical research then underway in many universities and hospitals. After Dr. Bush's proposal was accepted, the OSRD, going out of existence, turned over to NIH its funds to be used as grants to complete some 250 research projects in progress at universities, medical schools, and pharmaceutical companies.

The high-level decision to transfer the grants to NIH not only confirmed our role as the principal biomedical research arm of the Federal Government, but it also established extramural grants as a powerful mechanism for the support of such research.

In a report written in 1945, titled "Science--The Endless Frontier," Dr. Bush outlined the policy that has served the National interest so well in succeeding years. In recommending that the Government continue to support research in non-Federal laboratories, he asserted that: "The publicly and privately-supported colleges, universities and research institutes are centers of basic research. They are wellsprings of knowledge and understanding. As long as they are vigorous and healthy, and



their scientists are free to pursue the truth wherever it may lead, there will be a flow of new scientific knowledge."<sup>3</sup>

I should like to point out parenthetically that recognition of the importance of universities as the wellsprings of knowledge was also the cornerstone of the establishment of the Research Triangle. The presence of Duke University in Durham, North Carolina State University in Raleigh, and the University of North Carolina in Chapel Hill has been a critical element in the success of the Triangle and of NIEHS. This academic environment provides the opportunity for NIEHS scientists to continue to teach, maintaining their academic credentials, and provides the opportunity for budding young professionals to work in NIEHS laboratories on the most current problems in environmental health.

As far back as the 1940s, there had been an understanding that a critical element in scientific progress is our ability to continually renew the body of first-class scientists who can, and will, apply their creative energies to the search for knowledge. At the heart of many of our policy considerations in the 1940s -- and just as strongly today -- is the concern that we must make careers in medical research attractive and feasible.

In the very short period of five years, from 1940 to 1945, the NIH changed from a small Federal laboratory, whose activities were almost entirely in-house, to an agency whose focus turned increasingly to the support of research in non-Federal institutions.

In 1944 -- another important year in NIH history -- Congress passed the Public Health Service Act, providing the Surgeon General with broad-based authority to organize and conduct clinical research into "the causes, diagnosis, treatment, control, and prevention of physical and mental diseases and impairments of man, including water pollution, sewage treatment, and pollution of lakes and streams."

Addition of the extramural dimension to the NIH was accompanied by an increase in budget, and continuing increases that have been spectacular. In terms of purchasing power in constant dollars, the total budget of NIH

grew from 1945 to 1968 at an astounding average rate of 24 percent per year. The growth per year since 1968, taking inflation into account, has been much less -- about 2 percent per year.

The extremely rapid growth of the budget in the earlier period resulted, in part, from expansion of the scope of the agency through the creation, one by one, of new institutes. There are now 12 institutes, most of them oriented to specific organ systems or to families of disease, as for example, the National Heart, Lung, and Blood Institute; the National Eye Institute; the National Cancer Institute; and the National Institute of Allergy and Infectious Diseases.

The National Institute of Environmental Health Sciences carries an important distinction: it is a non-categorical Institute. Rather than focus on a particular disease or organ system, as do most of the rest of the Institutes, it focuses upon the effects of chemicals found in the environment on human health. In this way, its foundation reflects the latest of the Public Health Service Act and its specific language authorizing research into pollution.

The need for such an Institute was recognized as early as 1958, in the Bayne-Jones Report to Congress. Two years later, a Public Health Service Study Group wrote that environmental health problems would require increased efforts on the part of Government and the private sector. The report predicted the need for a central laboratory facility to develop the knowledge that would be needed to face the problems ahead.

Hardly a day goes by when we aren't reminded by a newspaper story or a television report of the wisdom of the decision to establish NIEHS. Last month we read of the accidental dumping of 30 tons of agricultural chemicals--herbicides, insecticides, and fungicides, some containing mercury--into the Rhine River killing half a million fish. These waters pass through four countries.

In our own country, the disposal of toxic waste remains an unsolved problem. There are thousands of hazardous waste dump sites across the

country threatening our groundwater supplies. Earlier this month, the Washington Post reported that waste from one of the most notorious of these sites, the Stringfellow Acid Pits in California, is once more creeping toward an underground water source that serves millions of people.

The NIEHS research is critical to developing an approach to such problems. It helps society characterize the threat to our health from environmental hazards, develop an understanding of the mechanisms by which agents act on the body, and validate methods for assessing the risk of these hazards.

I know scientists from this Institute have been in the forefront of research on PCBs, PBBs, metals, DES, and dioxin. I found the range of subjects of the scientific presentations Wednesday and Thursday fascinating.

I also know that there is a great deal more that remains to be understood about the 50,000 chemicals in the environment, most of which are inadequately tested. Much remains to be understood about intraspecies differences, low level effects, and the effects of mixtures. Your Task Force Three report is very helpful in outlining the many unsolved problems.

In order to answer these questions -- and, in the process, to raise new ones, science being the kind of process that it is -- NIEHS was created as a Division of NIH on November 1, 1966. It was elevated to Institute status on January 12, 1969.

Thus, we have seen how the National Institutes of Health grew from a little laboratory on States Island to a \$6 billion international scientific enterprise. But NIH is more than budgets and buildings. It is a creative spirit, a drive to greater understanding of the biological forces that are so important to our destiny. The following speakers will show how NIEHS is a part of that scientific enterprise and how it grew from a dream to a magnificent reality.

I would like to close with this thought. Vannevar Bush said, "Scientific progress results from the free play of free intellects working

on subjects of their own choice, in the manner dictated by their curiosity for exploration of the unknown." It is on this philosophical foundation that the research support programs of the National Institutes of Health were established and have continued to flourish.

Thank you.

#### REFERENCES

<sup>1</sup>Furman, Bess, A Profile of the United States Public Health Service 1798-1948, U.S. Government Printing Office, Washington, DC, 1973, p. 196.

<sup>2</sup>Furman, Bess, A Profile of the United States Public Health Service 1798-1948, U.S. Government Printing Office, Washington, DC, 1973, p. 203.

<sup>3</sup>Bush, Vannevar, Science--The Endless Frontier, Report to the President on a program for postwar scientific research, 1945, p. 7.

<sup>4</sup>Bush, Vannevar, Science--The Endless Frontier, Report to the President on a program for postwar scientific research, 1945, p. 7.



11  
23  
(4)











Amazing Research.  
Amazing Help.

<http://nihlibrary.nih.gov>

10 Center Drive  
Bethesda, MD 20892-1150  
301-496-1080







3 1496 00585 4743